Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Perspective:

MicroRNAs in the regulation of immune response against infections

Yue ZHANG[†1], Ying-ke LI[2]
([1]*Department of General Surgery, East Hospital, Tongji University School of Medicine, Shanghai 200120, China*)
([2]*Department of Anesthesiology, Changzheng Hospital, the Second Military Medical University, Shanghai 200003, China*)
[†]E-mail: magiczhangyue@yahoo.com.cn
Received Oct. 30, 2012; Revision accepted Nov. 7, 2012
Crosschecked Dec. 10, 2012

doi:10.1631/jzus.B1200292
Document code: A **CLC number:** R392.11

Innate immunity is considered to provide the initial defense against infections by viruses, bacteria, fungi, and protozoa. Detection of the signature molecules of invading pathogens by front-line defense cells via various germline-encoded pattern recognition receptors (PRRs) is needed to activate intracellular signaling cascades that lead to transcriptional expression of inflammatory mediators to coordinate the elimination of pathogens and infected cells. To maintain a fine balance between protective immunity and inflammatory pathology upon infection, the innate signaling pathways in the host need to be tightly regulated. MicroRNAs (miRNAs), a new class of small non-coding RNAs, have been recently shown to be potent modulators that function at post-transcriptional levels. Accumulating evidence demonstrates that the involvement of microorganism-encoded and host miRNAs might play instructive roles in the immune response upon infection. Here, we discuss the current knowledge of miRNAs in the regulation of immune response against infections.

1 Introduction

MicroRNAs (miRNAs) are a class of 19 to 24 nucleotides (nt) noncoding RNAs transcribed from the genomes of all multicellular organisms and some viruses. During this decade, there has been a tremendous increase in the number of miRNAs discovered in organisms (O′Neill *et al*., 2011). Their roles have been described in development, defense, and apoptosis. More than 30% of protein-coding genes are thought to be regulated by miRNAs at the post transcriptional and translational levels. miRNAs are initially transcribed by RNA polymerase II in the nucleus as primary miRNAs (pri-miRNAs). The pri-miRNA may contain one or several stem-loop structures that are cleaved by the nuclear RNaseIII type enzyme Drosha to produce a short hairpin precursor miRNA (pre-miRNA) transcript which can be shuttled into the cytoplasm. Pre-miRNA is finally matured by Dicer in the cytoplasm into the functional 22-base-pair (bp) double-stranded RNA (dsRNA), which is incorporated into the RNA-induced silencing complex (RISC) and forms the mature miRNA. Recent findings have shown that the majority of miRNA binding sites are in the 3′ untranslated region (3′ UTR) of target mRNA molecules and target interaction results in the degradation of the mRNA or translation repression (Alam and O′Neill, 2011).

Upon infection, sentinel cells such as neutrophils, macrophages, and dendritic cells (DCs), detect various invading pathogens through germline-encoded pattern recognition receptors (PRRs), which sense invariant microbial components termed pathogen-associated molecular patterns (PAMPs) derived from viruses, bacteria, fungi, and parasitic-protozoa (Takeuchi and Akira, 2010). Toll-like receptors (TLRs) represent the most studied PRRs and multiple aspects of the immune response have been shown to be controlled by TLRs. Besides TLRs, many other PRR families have been described, including retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), Nod-like receptors (NLRs), and C-type lectin receptors (CLRs) (Desmet and Ishii, 2012; Hardison and Brown, 2012). PRR signals elicit signaling cascades, including those mediated by mitogen-activated protein kinases (MAPKs), nuclear factor-κB (NF-κB), and interferon

regulatory factors (IRFs), which lead to up-regulation of type I interferons and proinflammatory cytokines that orchestrate innate and adaptive immunities to infection. Some NLRs assemble in inflammasomes, which control the activation of the cysteine protease caspase-1, and subsequent processing of interleukin (IL)-1β and IL-18 (Rathinam *et al*., 2012). However, PRR activation is a double-edged sword, as it is essential for provoking the innate response and enhancing adaptive immunity against pathogens, while inappropriate activation can also result in pathological inflammation as well as diseases. There is growing evidence to indicate that PRR signaling and functions need to be tightly regulated and many molecules have been identified as positive or negative regulators of immune response against infections (Qian and Cao, 2012).

Recent reports also throw light into the role of miRNAs as critical effectors in the regulation of host-pathogen interaction networks (O′Connell *et al*., 2012). The involvement of some miRNAs might be a part of a host response to an infection to dissemination of the microorganism or limit replication. Interestingly, the host miRNA pathway could also be manipulated by the microorganism to facilitate its replication. Understanding how the immune response is regulated by miRNAs during infection will obviously facilitate the development of new strategies to control PRR-mediated inflammatory diseases. In this paper, we comprehensively review the recent progress in the field of the regulation of immune response against infections by miRNAs.

2 miRNAs in the regulation of immune response against viral infection

RLRs and TLRs are the two major receptor systems employed by the host for detecting RNA virus infection and evoking antiviral responses by producing type I interferons (IFNs). Many positive or negative regulators of this process, such as neuregulin receptor degradation protein 1 (Nrdp1) (Wang *et al.*, 2009), constitutive heat shock cognate 70 (HSC70)-interacting protein (CHIP) (Yang *et al.*, 2011), SH2-containing protein tyrosine phosphatase 1 (SHP-1) (An *et al.*, 2008)/SHP-2 (An *et al.*, 2006), and β-catenin (Yang *et al.*, 2010), have been characterized. Recently, miRNAs have emerged to be involved in the host immunity to virus invasion, or in virus infection to create favorable intracellular environments for virus replication (Skalsky and Cullen, 2010).

Some viral miRNAs have been discovered recently to regulate viral gene expression through degradation of viral transcripts. For example, Epstein-Barr virus (EBV)-encoded miRNA miR-BART2 guides cleavage within the 3′ UTR of the viral DNA polymerase BALF5 by virtue of its complete complementarity to its target, which is compatible with the notion that EBV-miR-BART2 inhibits transition from latent to lytic viral replication (Barth *et al*., 2008).

Recent reports suggest that some viral miRNAs regulate host gene expression by engaging in novel regulatory relationships or by mimicking cellular miRNAs, and thereby utilizing predefined cellular regulatory networks. It has been recently reported that human cytomegalovirus (HCMV) can use a virus-coded miRNA miR-112-1-mediated suppression of the viral immediate-early protein 1 mRNA as part of its strategy to enter and maintain latency (Murphy *et al.*, 2008). miR-K12-11 miRNA encoded by Kaposi's sarcoma-associated herpes virus (KSHV) is an ortholog of cellular miR-155 and is probably evolved to exploit a pre-existing gene regulatory pathway in B cells, contributing to the induction of B-cell tumours in infected patients (Gottwein *et al.*, 2007).

Conversely, cellular miRNAs can also affect viral replication and pathogenesis, strikingly exemplified by the fact that host miR-122 facilitates hepatitis C virus (HCV) replication (Randall *et al*., 2007). Moreover, Triboulet *et al.* (2007) have recently found that human immunodeficiency virus type 1 (HIV-1) infection actively suppresses the expression of cellular miR-17/92 that represses viral replication via the histone acetyltransferase Tat cofactor p300/CBP-associated factor (PCAF). Infection of vesicular stomatitis virus (VSV) in macrophages induces miR-146a expression in an RIG-I dependent manner, and then miR-146a suppresses VSV-triggered type I IFN production by targeting IL-1 receptor-associated kinase 1 (IRAK1), IRAK2, and tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) so as to

promote VSV replication (Hou *et al.*, 2009). By targeting p300, miR-132 has been shown to be highly up-regulated after herpes simplex virus-1 (HSV-1), KSHV, or HCMV infection, and has a negative effect on the expression of IFN-stimulated genes, facilitating viral replication (Lagos *et al.*, 2010).

There is mounting evidence that the production of type I IFN is critical for the antimicrobial response. Recently, it has also been shown that miR-466l can directly bind to the 3′ UTR of IFN-α and reduce its expression during VSV infection (Li *et al.*, 2012). Type I IFN is also involved in the manipulation of miRNA expression. For example, IFN-α activation has been shown to suppress miR-378 and miR-30e expression to release cytolytic molecule mRNAs for their protein translation and then augment natural killer (NK) cell cytotoxicity (Wang P. *et al*., 2012). Induction of miR-155 by VSV infection has been shown to suppress suppressor of cytokine signaling 1 (SOCS1) expression in macrophages and subsequently enhance type I IFN effector gene expression and type I IFN-mediated antiviral response, thus suppressing viral replication (Wang *et al.*, 2010).

3 miRNAs in the regulation of immune response against bacterial infection

The realization that TLR sensing of bacterial components contributes to the onset of many clinical features of sepsis reinforces the interest of immunologists in PRRs. TLR signalling can be broadly divided into two pathways: the myeloid differentiation primary response gene (88) (MyD88)-dependent and Toll/IL-1 receptor domain-containing adaptor inducing IFN-β (TRIF)-dependent pathways (Netea *et al*., 2012). Many factors have been identified as being essential for full activation of TLR responses, such as major histocompatibility complex class II (MHCII) (Liu *et al.*, 2011), CMRF-35-like molecule 3 (CLM-3) (Wu *et al.*, 2011), heat shock protein 70 (HSP70) (Chen *et al.*, 2009)/HSP70L1 (Fang *et al.*, 2011), and nerve growth factor (NGF) (Jiang *et al.*, 2007). There is also evidence that many molecules can negatively regulate TLR signaling, such as Src homology 2 domain-containing inositol-5-phosphatase 1 (SHIP1) (An *et al.*, 2005), protein-tyrosine phosphatase 1B (PTP1B) (Xu *et al.*, 2008), cluster of differentiation molecule 11b (CD11b) (Han *et al.*, 2010), platelet endothelial cell adhesion molecule 1 (PECAM-1) (Rui *et al.*, 2007), Rab7b (Wang *et al.*, 2007; Yao *et al.*, 2009), and MHCI (Xu *et al.*, 2012). Several miRNAs are induced by TLR activation in innate immune cells and have emerged as important controllers of TLR signalling.

Multiple miRNAs are induced in innate immune cells, with a consensus emerging that miR-155, miR-146, and miR-223 are particularly up-regulated and target TLR signalling proteins during bacterical infection. miR-155 has been demonstrated to increase during maturation of human monocyte-derived DCs after exposure to lipopolysaccharides (LPS) and directly target PU.1 mRNA (Hu *et al.*, 2010). Upon *Helicobacter pylori* infection, the induced miR-155 has also been identified to target MyD88 (Tang *et al.*, 2010). In human monocyte-derived DCs, miR-155 is identified to target transforming growth factor β-activated kinase 1-binding protein 2 (TAB2), a signal molecule downstream of TRAF6 which activates MAPK kinases (Ceppi *et al.*, 2009). Inhibition of miR-155 leads to elevated activation of p38 pathway. miR-155 can also directly target the transcription factor Foxp3 (Kohlhaas *et al.*, 2009). Exposure of cultured macrophages and mice to LPS could lead to up-regulation of miR-155 and that the transcription factor c/ebp β is a direct target of miR-155 during inflammatory responses (Worm *et al.*, 2009). In addition, miR-155 could directly target several molecules involved in TLR4 signaling, such as the Fas-associated death domain protein (FADD), IκB kinase ε (IKKε), and the receptor (TNF receptor (TNFR) superfamily)-interacting serine-threonine kinase 1 (Ripk1) while enhancing TNF-α translation (Tili *et al.*, 2007). miR-146a was found to repress two key adapter molecules downstream of TLRs: IRAK1 and TRAF6 (Taganov *et al.*, 2006). TLR9-triggered miR-146a up-regulation has also been identified to target Notch1 in DCs, which is responsible for the reduced IL-12p70 production, subsequently promoting DC cross-priming of the cytotoxic T-lymphocyte (CTL) response (Bai *et al.*, 2012). Recently, IRAK2 has also been confirmed as a target of miR-146 (Wang L.L. *et al.*, 2012). miR-223 has been found to

be dramatically decreased during human monocyte-macrophage differentiation, leading to increased expression of the serine-threonine kinase IKKα in macrophages (Li *et al.*, 2010). Recently, Chen *et al.* (2012) demonstrated that inducible miRNA-223 down-regulation promotes TLR-triggered IL-6 and IL-1β production in macrophages by targeting STAT3. Inhibiting the activity of miR-223 has also been shown to decrease LPS-induced IFN-γ in splenic lymphocytes from estrogen-treated mice (Dai *et al.*, 2008).

Many other miRNAs have also been demonstrated to target certain components of the TLR signalling pathway by certain miRNAs. miRNA-148/152 can regulate the innate response and antigen presentation of TLR-triggered DCs by targeting CaMKIIα (Liu *et al.*, 2008; 2010). More recently, miR-466l has been shown to up-regulate IL-10 expression of both mRNA and protein levels in TLR-triggered macrophages by antagonizing the RNA-binding protein tristetraprolin mediated IL-10 mRNA degradation (Ma *et al.*, 2010). Ma *et al.* (2011) found that infection of mice with *Listeria monocytogenes* or *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) down-regulated miR-29 expression which subsequently suppressed immune responses by directly targeting IFN-γ.

4 miRNAs in the regulation of immune response against parasite infection

Evidence is accumulating that the miRNAs are implicated in the course and outcome of parasite infection. miR-27b has recently been shown to target KH-type splicing regulatory protein (KSRP) and modulate inducible nitric oxide synthase (iNOS) mRNA stability, a process that may be relevant to the regulation of anti-microbial defense from epithelial cells infected with *Cryptosporidium*, a protozoan parasite that infects the gastrointestinal epithelium and causes a diarrheal disease (Zhou *et al.*, 2012). In addition, human miR-17 family members have been found to increase upon infection with the intracellular parasite *Toxoplasma gondii*, while the detailed information about the direct intervention of parasites in the alteration of host miRNA levels and how this is regulated by parasites at molecular levels is still lacking (Zeiner and Boothroyd, 2010).

5 Conclusions

miRNAs are "fine-tuners" of the immune response against multiple infections. Both pathogenic specific miRNA sequences and the phenomenon of the alteration of host miRNA levels after infection are known and further added a new layer of complexity to the area of post-transcriptional regulation in the area of innate immunity. Because of the ability of miRNAs to function as key regulators of the gene expression, it is not surprising that aberrant miRNA expression has been implicated in several infectious diseases, providing the prospective uses of miRNAs as clinical non-invasive biomarkers. Furthermore, the possibility for a relatively easy manipulation of the miRNA machinery and the apparent lack of adverse events when administered place miRNAs as promising targets for the treatment of infections.

References

Alam, M.M., O′Neill, L.A., 2011. MicroRNAs and the resolution phase of inflammation in macrophages. *Eur. J. Immunol.*, **41**(9):2482-2485. [doi:10.1002/eji.201141740]

An, H., Xu, H., Zhang, M., Zhou, J., Feng, T., Qian, C., Qi, R., Cao, X., 2005. Src homology 2 domain-containing inositol-5-phosphatase 1 (SHIP1) negatively regulates TLR4-mediated LPS response primarily through a phosphatase activity- and PI-3K-independent mechanism. *Blood*, **105**(12):4685-4692. [doi:10.1182/blood-2005-01-0191]

An, H., Zhao, W., Hou, J., Zhang, Y., Xie, Y., Zheng, Y., Xu, H., Qian, C., Zhou, J., Yu, Y., *et al*., 2006. SHP-2 phosphatase negatively regulates the TRIF adaptor protein-dependent type I interferon and proinflammatory cytokine production. *Immunity*, **25**(6):919-928. [doi:10.1016/j.immuni.2006.10.014]

An, H., Hou, J., Zhou, J., Zhao, W., Xu, H., Zheng, Y., Yu, Y., Liu, S., Cao, X., 2008. Phosphatase SHP-1 promotes TLR- and RIG-I-activated production of type I interferon by inhibiting the kinase IRAK1. *Nat. Immunol.*, **9**(5):542-550. [doi:10.1038/ni.1604]

Bai, Y., Qian, C., Qian, L., Ma, F., Hou, J., Chen, Y., Wang, Q., Cao, X., 2012. Integrin CD11b negatively regulates TLR9-triggered dendritic cell cross-priming by upregulating microRNA-146a. *J. Immunol.*, **188**(11):5293-5302. [doi:10.4049/jimmunol.1102371]

Barth, S., Pfuhl, T., Mamiani, A., Ehses, C., Roemer, K.,

Kremmer, E., Jaker, C., Hock, J., Meister, G., Grasser, F.A., 2008. Epstein-Barr virus-encoded microRNA miR-BART2 down-regulates the viral DNA polymerase BALF5. *Nucleic Acids Res.*, **36**(2):666-675. [doi:10.1093/nar/gkm1080]

Ceppi, M., Pereira, P.M., Dunand-Sauthier, I., Barras, E., Reith, W., Santos, M.A., Pierre, P., 2009. MicroRNA-155 modulates the interleukin-1 signaling pathway in activated human monocyte-derived dendritic cells. *PNAS*, **106**(8):2735-2740. [doi:10.1073/pnas.0811073106]

Chen, Q., Wang, H., Liu, Y., Song, Y., Lai, L., Han, Q., Cao, X., Wang, Q., 2012. Inducible microRNA-223 down-regulation promotes TLR-triggered IL-6 and IL-1β production in macrophages by targeting STAT3. *PLoS One*, **7**(8):e42971. [doi:10.1371/journal.pone. 0042971]

Chen, T., Guo, J., Han, C., Yang, M., Cao, X., 2009. Heat shock protein 70, released from heat-stressed tumor cells, initiates antitumor immunity by inducing tumor cell chemokine production and activating dendritic cells via TLR4 pathway. *J. Immunol.*, **182**(3):1449-1459.

Dai, R., Phillips, R.A., Zhang, Y., Khan, D., Crasta, O., Ahmed, S.A., 2008. Suppression of LPS-induced interferon-γ and nitric oxide in splenic lymphocytes by select estrogen-regulated microRNAs: a novel mechanism of immune modulation. *Blood*, **112**(12):4591-4597. [doi:10.1182/blood-2008-04-152488]

Desmet, C.J., Ishii, K.J., 2012. Nucleic acid sensing at the interface between innate and adaptive immunity in vaccination. *Nat. Rev. Immunol.*, **12**(7):479-491. [doi:10.1038/nri3247]

Fang, H., Wu, Y., Huang, X., Wang, W., Ang, B., Cao, X., Wan, T., 2011. Toll-like receptor 4 (TLR4) is essential for Hsp70-like protein 1 (HSP70L1) to activate dendritic cells and induce Th1 response. *J. Biol. Chem.*, **286**(35):30393-30400. [doi:10.1074/jbc.M111.266528]

Gottwein, E., Mukherjee, N., Sachse, C., Frenzel, C., Majoros, W.H., Chi, J.T., Braich, R., Manoharan, M., Soutschek, J., Ohler, U., *et al*., 2007. A viral microRNA functions as an orthologue of cellular miR-155. *Nature*, **450**(7172):1096-1099. [doi:10.1038/nature05992]

Han, C., Jin, J., Xu, S., Liu, H., Li, N., Cao, X., 2010. Integrin CD11b negatively regulates TLR-triggered inflammatory responses by activating Syk and promoting degradation of MyD88 and TRIF via Cbl-b. *Nat. Immunol.*, **11**(8):734-742. [doi:10.1038/ni.1908]

Hardison, S.E., Brown, G.D., 2012. C-type lectin receptors orchestrate antifungal immunity. *Nat. Immunol.*, **13**(9):817-822. [doi:10.1038/ni.2369]

Hou, J., Wang, P., Lin, L., Liu, X., Ma, F., An, H., Wang, Z., Cao, X., 2009. MicroRNA-146a feedback inhibits RIG-I-dependent type I IFN production in macrophages by targeting TRAF6, IRAK1, and IRAK2. *J. Immunol.*, **183**(3):2150-2158. [doi:10.4049/jimmunol.0900707]

Hu, Y.L., Fong, S., Largman, C., Shen, W.F., 2010. HOXA9 regulates miR-155 in hematopoietic cells. *Nucleic Acids Res.*, **38**(16):5472-5478. [doi:10.1093/nar/gkq337]

Jiang, Y., Chen, G., Zhang, Y., Lu, L., Liu, S., Cao, X., 2007. Nerve growth factor promotes TLR4 signaling-induced maturation of human dendritic cells in vitro through inducible p75NTR 1. *J. Immunol.*, **179**(9):6297-6304.

Kohlhaas, S., Garden, O.A., Scudamore, C., Turner, M., Okkenhaug, K., Vigorito, E., 2009. Cutting edge: the Foxp3 target miR-155 contributes to the development of regulatory T cells. *J. Immunol.*, **182**(5):2578-2582. [doi:10.4049/jimmunol.0803162]

Lagos, D., Pollara, G., Henderson, S., Gratrix, F., Fabani, M., Milne, R.S., Gotch, F., Boshoff, C., 2010. miR-132 regulates antiviral innate immunity through suppression of the p300 transcriptional co-activator. *Nat. Cell Biol.*, **12**(5):513-519. [doi:10.1038/ncb2054]

Li, T., Morgan, M.J., Choksi, S., Zhang, Y., Kim, Y.S., Liu, Z.G., 2010. MicroRNAs modulate the noncanonical transcription factor NF-κB pathway by regulating expression of the kinase IKKα during macrophage differentiation. *Nat. Immunol.*, **11**(9):799-805. [doi:10.1038/ni.1918]

Li, Y., Fan, X., He, X., Sun, H., Zou, Z., Yuan, H., Xu, H., Wang, C., Shi, X., 2012. MicroRNA-466l inhibits antiviral innate immune response by targeting interferon-α. *Cell Mol. Immunol.*, **9**(6):497-502. [doi:10.1038/cmi.2012.35]

Liu, X., Yao, M., Li, N., Wang, C., Zheng, Y., Cao, X., 2008. CaMKII promotes TLR-triggered proinflammatory cytokine and type I interferon production by directly binding and activating TAK1 and IRF3 in macrophages. *Blood*, **112**(13):4961-4970. [doi:10.1182/blood-2008-03-144022]

Liu, X., Zhan, Z., Xu, L., Ma, F., Li, D., Guo, Z., Li, N., Cao, X., 2010. MicroRNA-148/152 impair innate response and antigen presentation of TLR-triggered dendritic cells by targeting CaMKIIα. *J. Immunol.*, **185**(12):7244-7251. [doi:10.4049/jimmunol.1001573]

Liu, X., Zhan, Z., Li, D., Xu, L., Ma, F., Zhang, P., Yao, H., Cao, X., 2011. Intracellular MHC class II molecules promote TLR-triggered innate immune responses by maintaining activation of the kinase Btk. *Nat. Immunol.*, **12**(5):416-424. [doi:10.1038/ni.2015]

Ma, F., Liu, X., Li, D., Wang, P., Li, N., Lu, L., Cao, X., 2010. MicroRNA-466l upregulates IL-10 expression in TLR-triggered macrophages by antagonizing RNA-binding protein tristetraprolin-mediated IL-10 mRNA degradation. *J. Immunol.*, **184**(11):6053-6059. [doi:10.4049/jimmunol.0902308]

Ma, F., Xu, S., Liu, X., Zhang, Q., Xu, X., Liu, M., Hua, M., Li, N., Yao, H., Cao, X., 2011. The microRNA miR-29 controls innate and adaptive immune responses to intracellular bacterial infection by targeting interferon-γ. *Nat. Immunol.*, **12**(9):861-869. [doi:10.1038/ni.2073]

Murphy, E., Vanicek, J., Robins, H., Shenk, T., Levine, A.J., 2008. Suppression of immediate-early viral gene expression by herpesvirus-coded microRNAs: implications for

latency. *PNAS*, **105**(14):5453-5458. [doi:10.1073/pnas.0711910105]

Netea, M.G., Wijmenga, C., O′Neill, L.A., 2012. Genetic variation in Toll-like receptors and disease susceptibility. *Nat. Immunol.*, **13**(6):535-542. [doi:10.1038/ni.2284]

O′Connell, R.M., Rao, D.S., Baltimore, D., 2012. MicroRNA regulation of inflammatory responses. *Annu. Rev. Immunol.*, **30**(1):295-312. [doi:10.1146/annurev-immunol-020711-075013]

O′Neill, L.A., Sheedy, F.J., McCoy, C.E., 2011. MicroRNAs: the fine-tuners of Toll-like receptor signalling. *Nat. Rev. Immunol*., **11**(3):163-175. [doi:10.1038/nri2957]

Qian, C., Cao, X., 2012. Regulation of Toll-like receptor signaling pathways in innate immune response. *Ann. N. Y. Acad. Sci.*, in press. [doi:10.1111/j.1749-6632.2012.06786.x]

Randall, G., Panis, M., Cooper, J.D., Tellinghuisen, T.L., Sukhodolets, K.E., Pfeffer, S., Landthaler, M., Landgraf, P., Kan, S., Lindenbach, B.D., *et al*., 2007. Cellular cofactors affecting hepatitis C virus infection and replication. *PNAS*, **104**(31):12884-12889. [doi:10.1073/pnas.0704894104]

Rathinam, V.A., Vanaja, S.K., Fitzgerald, K.A., 2012. Regulation of inflammasome signaling. *Nat. Immunol.*, **13**(4):333. [doi:10.1038/ni.2237]

Rui, Y., Liu, X., Li, N., Jiang, Y., Chen, G., Cao, X., Wang, J., 2007. PECAM-1 ligation negatively regulates TLR4 signaling in macrophages. *J. Immunol.*, **179**(11):7344-7351.

Skalsky, R.L., Cullen, B.R., 2010. Viruses, microRNAs, and host interactions. *Annu. Rev. Microbiol.*, **64**(1):123-141. [doi:10.1146/annurev.micro.112408.134243]

Taganov, K.D., Boldin, M.P., Chang, K.J., Baltimore, D., 2006. NF-κB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *PNAS*, **103**(33):12481-12486. [doi:10.1073/pnas.0605298103]

Takeuchi, O., Akira, S., 2010. Pattern recognition receptors and inflammation. *Cell*, **140**(6):805-820. [doi:10.1016/j.cell.2010.01.022]

Tang, B., Xiao, B., Liu, Z., Li, N., Zhu, E.D., Li, B.S., Xie, Q.H., Zhuang, Y., Zou, Q.M., Mao, X.H., 2010. Identification of MyD88 as a novel target of miR-155, involved in negative regulation of Helicobacter pylori-induced inflammation. *FEBS Lett*., **584**(8):1481-1486. [doi:10.1016/j.febslet.2010.02.063]

Tili, E., Michaille, J.J., Cimino, A., Costinean, S., Dumitru, C.D., Adair, B., Fabbri, M., Alder, H., Liu, C.G., Calin, G.A., *et al*., 2007. Modulation of miR-155 and miR-125b levels following lipopolysaccharide/TNF-α stimulation and their possible roles in regulating the response to endotoxin shock. *J. Immunol*., **179**(8):5082-5089.

Triboulet, R., Mari, B., Lin, Y.L., Chable-Bessia, C., Bennasser, Y., Lebrigand, K., Cardinaud, B., Maurin, T., Barbry, P., Baillat, V., *et al*., 2007. Suppression of microRNA-silencing pathway by HIV-1 during virus replication. *Science*, **315**(5818):1579-1582. [doi:10.1126/science.1136319]

Wang, C., Chen, T., Zhang, J., Yang, M., Li, N., Xu, X., Cao, X., 2009. The E3 ubiquitin ligase Nrdp1 'preferentially' promotes TLR-mediated production of type I interferon. *Nat. Immunol.*, **10**(7):744-752. [doi:10.1038/ni.1742]

Wang, L.L., Huang, Y., Wang, G., Chen, S.D., 2012. The potential role of microRNA-146 in Alzheimer's disease: biomarker or therapeutic target? *Med. Hypotheses*, **78**(3):398-401. [doi:10.1016/j.mehy.2011.11.019]

Wang, P., Hou, J., Lin, L., Wang, C., Liu, X., Li, D., Ma, F., Wang, Z., Cao, X., 2010. Inducible microRNA-155 feedback promotes type I IFN signaling in antiviral innate immunity by targeting suppressor of cytokine signaling 1. *J. Immunol.*, **185**(10):6226-6233. [doi:10.4049/jimmunol.1000491]

Wang, P., Gu, Y., Zhang, Q., Han, Y., Hou, J., Lin, L., Wu, C., Bao, Y., Su, X., Jiang, M., *et al*., 2012. Identification of resting and type I IFN-activated human NK cell miRNomes reveals microRNA-378 and microRNA-30e as negative regulators of NK cell cytotoxicity. *J. Immunol*., **189**(1):211-221. [doi:10.4049/jimmunol.1200609]

Wang, Y., Chen, T., Han, C., He, D., Liu, H., An, H., Cai, Z., Cao, X., 2007. Lysosome-associated small Rab GTPase Rab7b negatively regulates TLR4 signaling in macrophages by promoting lysosomal degradation of TLR4. *Blood*, **110**(3):962-971. [doi:10.1182/blood-2007-01-066027]

Worm, J., Stenvang, J., Petri, A., Frederiksen, K.S., Obad, S., Elmen, J., Hedtjarn, M., Straarup, E.M., Hansen, J.B., Kauppinen, S., 2009. Silencing of microRNA-155 in mice during acute inflammatory response leads to derepression of c/ebp β and down-regulation of G-CSF. *Nucleic Acids Res*., **37**(17):5784-5792. [doi:10.1093/nar/gkp577]

Wu, Y., Zhu, X., Li, N., Chen, T., Yang, M., Yao, M., Liu, X., Jin, B., Wang, X., Cao, X., 2011. CMRF-35-like molecule 3 preferentially promotes TLR9-triggered proinflammatory cytokine production in macrophages by enhancing TNF receptor-associated factor 6 ubiquitination. *J. Immunol.*, **187**(9):4881-4889. [doi:10.4049/jimmunol.1003806]

Xu, H., An, H., Hou, J., Han, C., Wang, P., Yu, Y., Cao, X., 2008. Phosphatase PTP1B negatively regulates MyD88- and TRIF-dependent proinflammatory cytokine and type I interferon production in TLR-triggered macrophages. *Mol. Immunol*., **45**(13):3545-3552. [doi:10.1016/j.molimm.2008.05.006]

Xu, S., Liu, X., Bao, Y., Zhu, X., Han, C., Zhang, P., Zhang, X., Li, W., Cao, X., 2012. Constitutive MHC class I molecules negatively regulate TLR-triggered inflammatory responses via the Fps-SHP-2 pathway. *Nat. Immunol.*, **13**(6):551-559. [doi:10.1038/ni.2283]

Yang, M., Wang, C., Zhu, X., Tang, S., Shi, L., Cao, X., Chen, T., 2011. E3 ubiquitin ligase CHIP facilitates Toll-like receptor signaling by recruiting and polyubiquitinating Src and atypical PKCζ. *J. Exp. Med*., **208**(10):

2099-2112. [doi:10.1084/jem.20102667]

Yang, P., An, H., Liu, X., Wen, M., Zheng, Y., Rui, Y., Cao, X., 2010. The cytosolic nucleic acid sensor LRRFIP1 mediates the production of type I interferon via a β-catenin-dependent pathway. *Nat. Immunol.*, **11**(6):487-494. [doi:10.1038/ni.1876]

Yao, M., Liu, X., Li, D., Chen, T., Cai, Z., Cao, X., 2009. Late endosome/lysosome-localized Rab7b suppresses TLR9-initiated proinflammatory cytokine and type I IFN production in macrophages. *J. Immunol.*, **183**(3):1751-1758. [doi:10.4049/jimmunol.0900249]

Zeiner, G.M., Boothroyd, J.C., 2010. Use of two novel approaches to discriminate between closely related host microRNAs that are manipulated by *Toxoplasma gondii* during infection. *RNA*, **16**(6):1268-1274. [doi:10.1261/rna.2069310]

Zhou, R., Gong, A.Y., Eischeid, A.N., Chen, X.M., 2012. miR-27b targets KSRP to coordinate TLR4-mediated epithelial defense against *Cryptosporidium parvum* infection. *PLoS Pathog.*, **8**(5):e1002702. [doi:10.1371/journal.ppat.1002702]