[Frontiers in Bioscience, Landmark, 26, 771-796, Jan 1, 2021]

Emerging roles of microRNAs in the regulation of Toll-like receptor (TLR)-signaling

Saswati Banerjee[1], Winston E. Thompson[1], Indrajit Chowdhury[2]

[1]Department of Physiology, Morehouse School of Medicine, Atlanta, GA, USA, [2]Department of Obstetrics and Gynecology, Morehouse School of Medicine, Atlanta, GA, USA

TABLE OF CONTENTS

1. ABSTRACT

Toll-like receptors (TLRs) are evolutionarily conserved molecules that detect exogenous and endogenous molecular patterns and trigger both the innate and adaptive immune systems to initiate a pathogen-specific immune response and eliminate the threat. However, sustained, or prolonged activation of the immune system disrupts immunological homeostasis and leads to chronic or acute inflammatory diseases. MicroRNAs (miRNAs) can intervene in the initiation and modulation of the complex immunoregulatory networks via regulating the expression of TLRs and multiple components of TLR-signaling pathways including signaling proteins, transcription factors, and cytokines. Moreover, the aberrant expression of TLRs can induce the expression of several miRNAs which in turn regulate the expression of TLR signaling components and TLR-induced cytokines. The present review aims to highlight the emerging roles of miRNA in the regulation of TLR signaling, the interaction between the miRNAs and TLRs, and their implication in inflammatory diseases.

2. INTRODUCTION

The immune system is a complex network of immune organs, cells, and soluble factors (cytokines) that act locally or systemically through an immediate (innate) inflammatory response by cytokines and phagocytes, and a specific tailored immune response through adaptive immune cells, or a regulated immune-tolerant response. The differing, and sometimes opposing, roles of the immune system are mediated by a complex interplay of intracellular and extracellular signaling pathways. Cells of the immune system participate in the protection of the host from invading pathogens, foreign antigens, and incipient tumor cells, and in development, maintenance of homeostasis, tissue repair and regeneration processes for wound healing (1). The innate immune system depends on the pattern recognizing receptors (PRRs), includes

components of the complement system and Toll-like receptors (TLRs) family. TLRs are membrane-associated innate-immune sensors that detect the external pathogen-associated molecular patterns (PAMPs) or the internal damage-associated molecular patterns (DAMPs) and execute subsequent immune cell response (2-4). TLRs, the most extensively studied PRRs, are type-I transmembrane glycoprotein receptors. TLRs consist of three structurally important domains namely an ectodomain consisting of hydrophobic leucine-rich repeat region (LRR) for ligand recognition/binding at N-terminus and formation of functional dimers to initiate the signaling cascade, a single transmembrane helix, and a conserved cytoplasmic Toll/Interleukin-1 (IL-1) receptor (TIR) domain at C-terminus required for the activation of downstream intracellular signal transduction pathways (5, 6). Interestingly, the extracellular ligand-binding domains of TLRs contain hydrophobic leucine-rich repeat motifs that form horseshoe-shaped solenoid structures and contain an extensive β-sheet on its concave surface, and numerous ligand-binding insertions (7). TLRs are distinguished based on their ligand specificity, signal transduction pathways, and subcellular localization (8). In mammals, ten human (TLR1-10), and 13 murine TLR protein subfamily (TLR1-9, TLR11-13) have been identified with a functional difference among humans and mice (5, 9-11). TLRs are functionally classified into two categories. The group I TLRs include TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10, and are expressed on the cell membrane and recognize microbially derived lipopolysaccharide (LPS) and lipopeptide ligands (12). The group II TLRs include TLR3, TLR7, TLR8, and TLR9, and are primarily expressed on vesicles and located intracellularly in the endoplasmic reticulum (ER), endosomes, and lysosomes compartments and recognize microbial nucleic acids released from stressed or dying cells (13-15). Unlike the other TLRs, TLR3 is expressed both on the cell surface and in intracellular vesicles and recognize viral dsRNA (16). Thus, TLRs are expressed in all tissues including macrophages, NK cells, DCs, circulating monocytes and neutrophils of the innate immune system; the adaptive immune cells (T and B lymphocytes), as well as non-immune cells and organs, e.g. epithelial and endothelial cells, fibroblasts, brain, skeletal muscle, heart, lung, small intestine, liver, pancreas, colon, kidney, ovary, placenta, testis and prostate (17, 18).

MicroRNAs (miRNAs) have received considerable attention due to their involvement in the post-transcriptional regulatory mechanisms in almost all known cellular processes including development, differentiation, apoptosis, and the innate and adaptive immune responses to pathogen infections (19-26). Besides, extracellular miRNAs secreted from the donor cells could be delivered into recipient cells via extracellular vesicles and exosomes to establish a cell-cell communication system during various physiological and pathological processes (27-32). Selective miRNA studies in context to the regulation of TLRs suggest that miRNAs can modulate TLR signaling either through their involvement via transcriptional regulation or serving as physiological ligands of TLRs. Moreover, studies suggest that miRNA expression can be directly regulated by TLRs pathway (33). Interestingly, TLR activation modulates the expression of miRNAs that regulate TLR signaling either by the direct targeting of the molecules in the TLR pathway or indirectly through altering the activity of other cellular pathways that participate in crosstalk. The present review is highlighting the implication of TLRs in diseases and the emerging roles of microRNA (miRNA) in regulation of TLRs signaling.

3. PATHOPHYSIOLOGY OF TLR-SIGNALING

TLRs are the cell-surface initiators that trigger the inflammatory process. TLRs recognize conserved microbial-associated molecular patterns including LPS (TLR4), diacyl and triacyl lipopeptides, and zymosan (TLR2 associated with TLR1 or TLR6), peptidoglycan and lipoarabinomannan (TLR2), bacterial flagellin (TLR5), viral dsRNA (TLR3), viral or bacterial ssRNA (TLRs 7 and 8), HMGB1 (TLR2 and TLR4), and CpG-rich unmethylated DNA (TLR9) among others (34-36) (Figure 1). Several TLRs require to

immune response and tissue repair in the CNS: emphasis on the critical role of the complement system. *Mol Immunol*, 40(2-4), 85-94 (2003)
DOI: 10.1016/s0161-5890(03)00109-3

5. K. Takeda, T. Kaisho and S. Akira: Toll-like receptors. *Annu Rev Immunol*, 21, 335-76 (2003)
DOI: 10.1146/annurev.immunol-.21.120601.141126

6. T. Kawai and S. Akira: The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol*, 11(5), 373-84 (2010)
DOI: 10.1038/ni.1863

7. J. K. Bell, G. E. Mullen, C. A. Leifer, A. Mazzoni, D. R. Davies and D. M. Segal: Leucine-rich repeats and pathogen recognition in Toll-like receptors. *Trends Immunol*, 24(10), 528-33 (2003)
DOI: 10.1016/s1471-4906(03)00242-4

8. K. Singh, S. Kant, V. K. Singh, N. K. Agrawal, S. K. Gupta and K. Singh: Toll-like receptor 4 polymorphisms and their haplotypes modulate the risk of developing diabetic retinopathy in type 2 diabetes patients. *Mol Vis*, 20, 704-13 (2014)

9. T. Kawai and S. Akira: Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity*, 34(5), 637-50 (2011)
DOI: 10.1016/j.immuni.2011.05.006

10. Y. Wang, E. Song, B. Bai and P. M. Vanhoutte: Toll-like receptors mediating vascular malfunction: Lessons from receptor subtypes. *Pharmacol Ther*, 158, 91-100 (2016)
DOI: 10.1016/j.pharmthera.2015.12.005

11. M. Yamamoto and K. Takeda: Current views of toll-like receptor signaling pathways. *Gastroenterol Res Pract*, 2010, 240365 (2010)
DOI: 10.1155/2010/240365

12. N. J. Gay, M. F. Symmons, M. Gangloff and C. E. Bryant: Assembly and localization of Toll-like receptor signalling complexes. *Nat Rev Immunol*, 14(8), 546-58 (2014)
DOI: 10.1038/nri3713

13. G. Sellge and T. A. Kufer: PRR-signaling pathways: Learning from microbial tactics. *Semin Immunol*, 27(2), 75-84 (2015)
DOI: 10.1016/j.smim.2015.03.009

14. A. F. McGettrick and L. A. O'Neill: Localisation and trafficking of Toll-like receptors: an important mode of regulation. *Curr Opin Immunol*, 22(1), 20-7 (2010)
DOI: 10.1016/j.coi.2009.12.002

15. T. Oosenbrug, M. J. van de Graaff, M. E. Ressing and S. I. van Kasteren: Chemical Tools for Studying TLR Signaling Dynamics. *Cell Chem Biol*, 24(7), 801-812 (2017)
DOI: 10.1016/j.chembiol.2017.05.022

16. M. Matsumoto and T. Seya: TLR3: interferon induction by double-stranded RNA including poly(I:C). *Adv Drug Deliv Rev*, 60(7), 805-12 (2008)
DOI: 10.1016/j.addr.2007.11.005

17. Y. Delneste, C. Beauvillain and P. Jeannin: [Innate immunity: structure and function of TLRs]. *Med Sci (Paris)*, 23(1), 67-73 (2007)
DOI: 10.1051/medsci/200723167

18. K. A. Zarember and P. J. Godowski: Tissue expression of human Toll-like receptors and differential regulation of Toll-like receptor mRNAs in leukocytes in response to microbes, their products, and cytokines. *J Immunol*, 168(2), 554-61 (2002)
DOI: 10.4049/jimmunol.168.2.554

19. G. A. Calin, C. G. Liu, C. Sevignani, M. Ferracin, N. Felli, C. D. Dumitru, M. Shimizu, A. Cimmino, S. Zupo, M. Dono, M. L. Dell'Aquila, H. Alder, L. Rassenti, T. J. Kipps, F. Bullrich, M. Negrini and C. M. Croce: MicroRNA profiling reveals distinct signatures in B cell chronic lymphocytic leukemias. *Proc Natl Acad Sci U S A*, 101(32), 11755-60 (2004)
DOI: 10.1073/pnas.0404432101

20. G. Di Leva, M. Garofalo and C. M. Croce: MicroRNAs in cancer. *Annu Rev Pathol*, 9, 287-314 (2014)
DOI: 10.1146/annurev-pathol-012513-104715

21. M. Fabbri, A. Paone, F. Calore, R. Galli and C. M. Croce: A new role for microRNAs, as ligands of Toll-like receptors. *RNA Biol*, 10(2), 169-74 (2013)
DOI: 10.4161/rna.23144

22. A. Mehta and D. Baltimore: MicroRNAs as regulatory elements in immune system logic. *Nat Rev Immunol*, 16(5), 279-94 (2016)
DOI: 10.1038/nri.2016.40

23. E. van Rooij and E. N. Olson: MicroRNA therapeutics for cardiovascular disease: opportunities and obstacles. *Nat Rev Drug Discov*, 11(11), 860-72 (2012)
DOI: 10.1038/nrd3864

24. D. P. Bartel: MicroRNAs: target recognition and regulatory functions. *Cell*, 136(2), 215-33 (2009)
DOI: 10.1016/j.cell.2009.01.002

25. M. R. Fabian, N. Sonenberg and W. Filipowicz: Regulation of mRNA translation and stability by microRNAs. *Annu Rev Biochem*, 79, 351-79 (2010)
DOI: 10.1146/annurev-biochem-060308-103103

26. C. Z. Chen, S. Schaffert, R. Fragoso and C. Loh: Regulation of immune responses and tolerance: the microRNA perspective. *Immunol Rev*, 253(1), 112-28 (2013)
DOI: 10.1111/imr.12060

27. R. Bayraktar, M. Pichler, P. Kanlikilicer, C. Ivan, E. Bayraktar, N. Kahraman, B. Aslan, S. Oguztuzun, M. Ulasli, A. Arslan, G. Calin, G. Lopez-Berestein and B. Ozpolat: MicroRNA 603 acts as a tumor suppressor and inhibits triple-negative breast cancer tumorigenesis by targeting elongation factor 2 kinase. *Oncotarget*, 8(7), 11641-11658 (2017)
DOI: 10.18632/oncotarget.14264

28. M. Fabbri, A. Paone, F. Calore, R. Galli, E. Gaudio, R. Santhanam, F. Lovat, P. Fadda, C. Mao, G. J. Nuovo, N. Zanesi, M. Crawford, G. H. Ozer, D. Wernicke, H. Alder, M. A. Caligiuri, P. Nana-Sinkam, D. Perrotti and C. M. Croce: MicroRNAs bind to Toll-like receptors to induce prometastatic inflammatory response. *Proc Natl Acad Sci U S A*, 109(31), E2110-6 (2012)
DOI: 10.1073/pnas.1209414109

29. V. Gonzalez-Villasana, M. H. Rashed, Y. Gonzalez-Cantu, R. Bayraktar, J. L. Menchaca-Arredondo, J. M. Vazquez-Guillen, C. Rodriguez-Padilla, G. Lopez-

Berestein and D. Resendez-Perez: Presence of Circulating miR-145, miR-155, and miR-382 in Exosomes Isolated from Serum of Breast Cancer Patients and Healthy Donors. *Dis Markers*, 2019, 6852917 (2019)
DOI: 10.1155/2019/6852917

30. S. M. Lehmann, C. Kruger, B. Park, K. Derkow, K. Rosenberger, J. Baumgart, T. Trimbuch, G. Eom, M. Hinz, D. Kaul, P. Habbel, R. Kalin, E. Franzoni, A. Rybak, D. Nguyen, R. Veh, O. Ninnemann, O. Peters, R. Nitsch, F. L. Heppner, D. Golenbock, E. Schott, H. L. Ploegh, F. G. Wulczyn and S. Lehnardt: An unconventional role for miRNA: let-7 activates Toll-like receptor 7 and causes neurodegeneration. *Nat Neurosci*, 15(6), 827-35 (2012)
DOI: 10.1038/nn.3113

31. M. H. Rashed, P. Kanlikilicer, C. Rodriguez-Aguayo, M. Pichler, R. Bayraktar, E. Bayraktar, C. Ivan, J. Filant, A. Silva, B. Aslan, M. Denizli, R. Mitra, B. Ozpolat, G. A. Calin, A. K. Sood, M. F. Abd-Ellah, G. K. Helal and G. L. Berestein: Exosomal miR-940 maintains SRC-mediated oncogenic activity in cancer cells: a possible role for exosomal disposal of tumor suppressor miRNAs. *Oncotarget*, 8(12), 20145-20164 (2017)
DOI: 10.18632/oncotarget.15525

32. M. L. Squadrito, C. Baer, F. Burdet, C. Maderna, G. D. Gilfillan, R. Lyle, M. Ibberson and M. De Palma: Endogenous RNAs modulate microRNA sorting to exosomes and transfer to acceptor cells. *Cell Rep*, 8(5), 1432-46 (2014)
DOI: 10.1016/j.celrep.2014.07.035

33. F. Olivieri, M. R. Rippo, F. Prattichizzo, L. Babini, L. Graciotti, R. Recchioni and A. D. Procopio: Toll like receptor signaling in "inflammaging": microRNA as new players. *Immun Ageing*, 10(1), 11 (2013)
DOI: 10.1186/1742-4933-10-11

34. K. Hoebe, X. Du, P. Georgel, E. Janssen, K. Tabeta, S. O. Kim, J. Goode, P. Lin, N. Mann, S. Mudd, K. Crozat, S. Sovath, J. Han and B. Beutler: Identification of Lps2 as a key transducer of MyD88-independent TIR signalling. *Nature*, 424(6950), 743-8 (2003)
DOI: 10.1038/nature01889

35. H. Kumar, T. Kawai and S. Akira: Pathogen recognition in the innate immune response. *Biochem J*, 420(1), 1-16 (2009)
DOI: 10.1042/BJ20090272

36. J. S. Ayres and D. S. Schneider: Tolerance of infections. *Annu Rev Immunol*, 30, 271-94 (2012)
DOI: 10.1146/annurev-immunol-020711-075030

37. C. C. Lee, A. M. Avalos and H. L. Ploegh: Accessory molecules for Toll-like receptors and their function. *Nat Rev Immunol*, 12(3), 168-79 (2012)
DOI: 10.1038/nri3151

38. C. A. Leifer and A. E. Medvedev: Molecular mechanisms of regulation of Toll-like receptor signaling. *J Leukoc Biol*, 100(5), 927-941 (2016)
DOI: 10.1189/jlb.2MR0316-117RR

39. I. Botos, D. M. Segal and D. R. Davies: The structural biology of Toll-like receptors. *Structure*, 19(4), 447-59 (2011)
DOI: 10.1016/j.str.2011.02.004

40. M. Carty, R. Goodbody, M. Schroder, J. Stack, P. N. Moynagh and A. G. Bowie:

The human adaptor SARM negatively regulates adaptor protein TRIF-dependent Toll-like receptor signaling. *Nat Immunol*, 7(10), 1074-81 (2006)
DOI: 10.1038/ni1382

41. E. F. Kenny and L. A. O'Neill: Signalling adaptors used by Toll-like receptors: an update. *Cytokine*, 43(3), 342-9 (2008)
DOI: 10.1016/j.cyto.2008.07.010

42. R. Barbalat, L. Lau, R. M. Locksley and G. M. Barton: Toll-like receptor 2 on inflammatory monocytes induces type I interferon in response to viral but not bacterial ligands. *Nat Immunol*, 10(11), 1200-7 (2009)
DOI: 10.1038/ni.1792

43. E. Faure, O. Equils, P. A. Sieling, L. Thomas, F. X. Zhang, C. J. Kirschning, N. Polentarutti, M. Muzio and M. Arditi: Bacterial lipopolysaccharide activates NF-kappaB through toll-like receptor 4 (TLR-4) in cultured human dermal endothelial cells. Differential expression of TLR-4 and TLR-2 in endothelial cells. *J Biol Chem*, 275(15), 11058-63 (2000)
DOI: 10.1074/jbc.275.15.11058

44. C. A. Janeway, Jr. and R. Medzhitov: Innate immune recognition. *Annu Rev Immunol*, 20, 197-216 (2002)
DOI: 10.1146/annurev.immunol.-20.083001.084359

45. M. S. Jin and J. O. Lee: Structures of the toll-like receptor family and its ligand complexes. *Immunity*, 29(2), 182-91 (2008)
DOI: 10.1016/j.immuni.2008.07.007

46. A. Mansell, E. Brint, J. A. Gould, L. A. O'Neill and P. J. Hertzog: Mal interacts with tumor necrosis factor receptor-associated factor (TRAF)-6 to mediate NF-kappaB activation by toll-like receptor (TLR)-2 and TLR4. *J Biol Chem*, 279(36), 37227-30 (2004)
DOI: 10.1074/jbc.C400289200

47. N. J. Bernard and L. A. O'Neill: Mal, more than a bridge to MyD88. *IUBMB Life*, 65(9), 777-86 (2013)
DOI: 10.1002/iub.1201

48. A. F. McGettrick, E. K. Brint, E. M. Palsson-McDermott, D. C. Rowe, D. T. Golenbock, N. J. Gay, K. A. Fitzgerald and L. A. O'Neill: Trif-related adapter molecule is phosphorylated by PKC{epsilon} during Toll-like receptor 4 signaling. *Proc Natl Acad Sci U S A*, 103(24), 9196-201 (2006)
DOI: 10.1073/pnas.0600462103

49. C. Couillault, N. Pujol, J. Reboul, L. Sabatier, J. F. Guichou, Y. Kohara and J. J. Ewbank: TLR-independent control of innate immunity in Caenorhabditis elegans by the TIR domain adaptor protein TIR-1, an ortholog of human SARM. *Nat Immunol*, 5(5), 488-94 (2004)
DOI: 10.1038/ni1060

50. T. D. Troutman, W. Hu, S. Fulenchek, T. Yamazaki, T. Kurosaki, J. F. Bazan and C. Pasare: Role for B-cell adapter for PI3K (BCAP) as a signaling adapter linking Toll-like receptors (TLRs) to serine/threonine kinases PI3K/Akt. *Proc Natl Acad Sci U S A*, 109(1), 273-8 (2012)
DOI: 10.1073/pnas.1118579109

51. N. W. Palm and R. Medzhitov: Pattern recognition receptors and control of adaptive immunity. *Immunol Rev*, 227(1), 221-33 (2009)
DOI: 10.1111/j.1600-065X.2008.00731.x

52. P. Broz and D. M. Monack: Newly described pattern recognition receptors

team up against intracellular pathogens. *Nat Rev Immunol*, 13(8), 551-65 (2013)
DOI: 10.1038/nri3479

53. X. He, Z. Jing and G. Cheng: MicroRNAs: new regulators of Toll-like receptor signalling pathways. *Biomed Res Int*, 2014, 945169 (2014)
DOI: 10.1155/2014/945169

54. K. Newton and V. M. Dixit: Signaling in innate immunity and inflammation. *Cold Spring Harb Perspect Biol*, 4(3) (2012)
DOI: 10.1101/cshperspect.a006049

55. Q. Q. Huang and R. M. Pope: The role of toll-like receptors in rheumatoid arthritis. *Curr Rheumatol Rep*, 11(5), 357-64 (2009)
DOI: 10.1007/s11926-009-0051-z

56. I. Jialal, H. Kaur and S. Devaraj: Toll-like receptor status in obesity and metabolic syndrome: a translational perspective. *J Clin Endocrinol Metab*, 99(1), 39-48 (2014)
DOI: 10.1210/jc.2013-3092

57. J. M. Isaza-Correa, Z. Liang, A. van den Berg, A. Diepstra and L. Visser: Toll-like receptors in the pathogenesis of human B cell malignancies. *J Hematol Oncol*, 7, 57 (2014)
DOI: 10.1186/s13045-014-0057-5

58. S. Devaraj, J. M. Yun, C. R. Duncan-Staley and I. Jialal: Low vitamin D levels correlate with the proinflammatory state in type 1 diabetic subjects with and without microvascular complications. *Am J Clin Pathol*, 135(3), 429-33 (2011)
DOI: 10.1309/AJCPJGZQX42BIAXL

59. L. A. O'Neill: When signaling pathways collide: positive and negative regulation of toll-like receptor signal transduction. *Immunity*, 29(1), 12-20 (2008)
DOI: 10.1016/j.immuni.2008.06.004

60. T. Kondo, T. Kawai and S. Akira: Dissecting negative regulation of Toll-like receptor signaling. *Trends Immunol*, 33(9), 449-58 (2012)
DOI: 10.1016/j.it.2012.05.002

61. J. J. Forman, A. Legesse-Miller and H. A. Coller: A search for conserved sequences in coding regions reveals that the let-7 microRNA targets Dicer within its coding sequence. *Proc Natl Acad Sci U S A*, 105(39), 14879-84 (2008)
DOI: 10.1073/pnas.0803230105

62. J. Zhang, W. Zhou, Y. Liu, T. Liu, C. Li and L. Wang: Oncogenic role of microRNA-532-5p in human colorectal cancer via targeting of the 5'UTR of RUNX3. *Oncol Lett*, 15(5), 7215-7220 (2018)
DOI: 10.3892/ol.2018.8217

63. E. V. Makeyev and T. Maniatis: Multilevel regulation of gene expression by microRNAs. *Science*, 319(5871), 1789-90 (2008)
DOI: 10.1126/science.1152326

64. A. Rebane and C. A. Akdis: MicroRNAs: Essential players in the regulation of inflammation. *J Allergy Clin Immunol*, 132(1), 15-26 (2013)
DOI: 10.1016/j.jaci.2013.04.011

65. A. Dharap, C. Pokrzywa, S. Murali, G. Pandi and R. Vemuganti: MicroRNA miR-324-3p induces promoter-mediated expression of RelA gene. *PLoS One*, 8(11), e79467 (2013)
DOI: 10.1371/journal.pone.0079467

66. F. Bullrich, H. Fujii, G. Calin, H. Mabuchi, M. Negrini, Y. Pekarsky, L. Rassenti, H. Alder, J. C. Reed, M. J. Keating, T. J. Kipps and C. M. Croce: Characterization of the 13q14 tumor suppressor locus in CLL: identification of ALT1, an alternative splice variant of the LEU2 gene. *Cancer Res*, 61(18), 6640-8 (2001)

67. M. Fabbri, R. Garzon, M. Andreeff, H. M. Kantarjian, G. Garcia-Manero and G. A. Calin: MicroRNAs and noncoding RNAs in hematological malignancies: molecular, clinical and therapeutic implications. *Leukemia*, 22(6), 1095-105 (2008)
DOI: 10.1038/leu.2008.30

68. P. Kanlikilicer, M. H. Rashed, R. Bayraktar, R. Mitra, C. Ivan, B. Aslan, X. Zhang, J. Filant, A. M. Silva, C. Rodriguez-Aguayo, E. Bayraktar, M. Pichler, B. Ozpolat, G. A. Calin, A. K. Sood and G. Lopez-Berestein: Ubiquitous Release of Exosomal Tumor Suppressor miR-6126 from Ovarian Cancer Cells. *Cancer Res*, 76(24), 7194-7207 (2016)
DOI: 10.1158/0008-5472.CAN-16-0714

69. R. Munker and G. A. Calin: MicroRNA profiling in cancer. *Clin Sci (Lond)*, 121(4), 141-58 (2011)
DOI: 10.1042/CS20110005

70. C. Sevignani, G. A. Calin, S. C. Nnadi, M. Shimizu, R. V. Davuluri, T. Hyslop, P. Demant, C. M. Croce and L. D. Siracusa: MicroRNA genes are frequently located near mouse cancer susceptibility loci. *Proc Natl Acad Sci U S A*, 104(19), 8017-22 (2007)
DOI: 10.1073/pnas.0702177104

71. L. A. Macfarlane and P. R. Murphy: MicroRNA: Biogenesis, Function and Role in Cancer. *Curr Genomics*, 11(7), 537-61 (2010)
DOI: 10.2174/138920210793175895

72. Y. Lee, C. Ahn, J. Han, H. Choi, J. Kim, J. Yim, J. Lee, P. Provost, O. Radmark, S. Kim and V. N. Kim: The nuclear RNase III Drosha initiates microRNA processing. *Nature*, 425(6956), 415-9 (2003)
DOI: 10.1038/nature01957

73. Y. Lee, K. Jeon, J. T. Lee, S. Kim and V. N. Kim: MicroRNA maturation: stepwise processing and subcellular localization. *EMBO J*, 21(17), 4663-70 (2002)
DOI: 10.1093/emboj/cdf476

74. M. Ballarino, F. Pagano, E. Girardi, M. Morlando, D. Cacchiarelli, M. Marchioni, N. J. Proudfoot and I. Bozzoni: Coupled RNA processing and transcription of intergenic primary microRNAs. *Mol Cell Biol*, 29(20), 5632-8 (2009)
DOI: 10.1128/MCB.00664-09

75. M. Morlando, M. Ballarino, N. Gromak, F. Pagano, I. Bozzoni and N. J. Proudfoot: Primary microRNA transcripts are processed co-transcriptionally. *Nat Struct Mol Biol*, 15(9), 902-9 (2008)
DOI: 10.1038/nsmb.1475

76. G. Hutvagner, J. McLachlan, A. E. Pasquinelli, E. Balint, T. Tuschl and P. D. Zamore: A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. *Science*, 293(5531), 834-8 (2001)
DOI: 10.1126/science.1062961

77. A. Grishok, A. E. Pasquinelli, D. Conte, N. Li, S. Parrish, I. Ha, D. L. Baillie, A. Fire, G. Ruvkun and C. C. Mello: Genes and mechanisms related to RNA interference regulate expression of the small temporal RNAs that control C. elegans

developmental timing. *Cell*, 106(1), 23-34 (2001)
DOI: 10.1016/s0092-8674(01)00431-7

78. R. F. Ketting, S. E. Fischer, E. Bernstein, T. Sijen, G. J. Hannon and R. H. Plasterk: Dicer functions in RNA interference and in synthesis of small RNA involved in developmental timing in C. elegans. *Genes Dev*, 15(20), 2654-9 (2001)
DOI: 10.1101/gad.927801

79. E. Bernstein, A. A. Caudy, S. M. Hammond and G. J. Hannon: Role for a bidentate ribonuclease in the initiation step of RNA interference. *Nature*, 409(6818), 363-6 (2001)
DOI: 10.1038/35053110

80. M. Yoda, T. Kawamata, Z. Paroo, X. Ye, S. Iwasaki, Q. Liu and Y. Tomari: ATP-dependent human RISC assembly pathways. *Nat Struct Mol Biol*, 17(1), 17-23 (2010)
DOI: 10.1038/nsmb.1733

81. J. O'Brien, H. Hayder, Y. Zayed and C. Peng: Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. *Front Endocrinol (Lausanne)*, 9, 402 (2018)
DOI: 10.3389/fendo.2018.00402

82. J. G. Ruby, C. H. Jan and D. P. Bartel: Intronic microRNA precursors that bypass Drosha processing. *Nature*, 448(7149), 83-6 (2007)
DOI: 10.1038/nature05983

83. J. E. Babiarz, J. G. Ruby, Y. Wang, D. P. Bartel and R. Blelloch: Mouse ES cells express endogenous shRNAs, siRNAs, and other Microprocessor-independent, Dicer-dependent small RNAs. *Genes Dev*, 22(20), 2773-85 (2008)
DOI: 10.1101/gad.1705308

84. K. Okamura, J. W. Hagen, H. Duan, D. M. Tyler and E. C. Lai: The mirtron pathway generates microRNA-class regulatory RNAs in Drosophila. *Cell*, 130(1), 89-100 (2007)
DOI: 10.1016/j.cell.2007.06.028

85. M. A. Havens, A. A. Reich, D. M. Duelli and M. L. Hastings: Biogenesis of mammalian microRNAs by a non-canonical processing pathway. *Nucleic Acids Res*, 40(10), 4626-40 (2012)
DOI: 10.1093/nar/gks026

86. M. Xie, M. Li, A. Vilborg, N. Lee, M. D. Shu, V. Yartseva, N. Sestan and J. A. Steitz: Mammalian 5'-capped microRNA precursors that generate a single microRNA. *Cell*, 155(7), 1568-80 (2013)
DOI: 10.1016/j.cell.2013.11.027

87. J. S. Yang, T. Maurin, N. Robine, K. D. Rasmussen, K. L. Jeffrey, R. Chandwani, E. P. Papapetrou, M. Sadelain, D. O'Carroll and E. C. Lai: Conserved vertebrate mir-451 provides a platform for Dicer-independent, Ago2-mediated microRNA biogenesis. *Proc Natl Acad Sci U S A*, 107(34), 15163-8 (2010)
DOI: 10.1073/pnas.1006432107

88. E. Huntzinger and E. Izaurralde: Gene silencing by microRNAs: contributions of translational repression and mRNA decay. *Nat Rev Genet*, 12(2), 99-110 (2011)
DOI: 10.1038/nrg2936

89. J. J. Ipsaro and L. Joshua-Tor: From guide to target: molecular insights into eukaryotic RNA-interference machinery. *Nat Struct Mol Biol*, 22(1), 20-8 (2015)
DOI: 10.1038/nsmb.2931

90. G. Fu, J. Brkic, H. Hayder and C. Peng: MicroRNAs in Human Placental

Development and Pregnancy Complications. *Int J Mol Sci*, 14(3), 5519-44 (2013)
DOI: 10.3390/ijms14035519

91. S. Lin and R. I. Gregory: MicroRNA biogenesis pathways in cancer. *Nat Rev Cancer*, 15(6), 321-33 (2015)
DOI: 10.1038/nrc3932

92. F. Wang, C. Chen and D. Wang: Circulating microRNAs in cardiovascular diseases: from biomarkers to therapeutic targets. *Front Med*, 8(4), 404-18 (2014)
DOI: 10.1007/s11684-014-0379-2

93. S. Absalon, D. M. Kochanek, V. Raghavan and A. M. Krichevsky: MiR-26b, upregulated in Alzheimer's disease, activates cell cycle entry, tau-phosphorylation, and apoptosis in postmitotic neurons. *J Neurosci*, 33(37), 14645-59 (2013)
DOI: 10.1523/JNEUROSCI.1327-13.2013

94. E. Minones-Moyano, S. Porta, G. Escaramis, R. Rabionet, S. Iraola, B. Kagerbauer, Y. Espinosa-Parrilla, I. Ferrer, X. Estivill and E. Marti: MicroRNA profiling of Parkinson's disease brains identifies early downregulation of miR-34b/c which modulate mitochondrial function. *Hum Mol Genet*, 20(15), 3067-78 (2011)
DOI: 10.1093/hmg/ddr210

95. R. M. O'Connell, D. S. Rao, A. A. Chaudhuri and D. Baltimore: Physiological and pathological roles for microRNAs in the immune system. *Nat Rev Immunol*, 10(2), 111-22 (2010)
DOI: 10.1038/nri2708

96. L. A. O'Neill, F. J. Sheedy and C. E. McCoy: MicroRNAs: the fine-tuners of Toll-like receptor signalling. *Nat Rev Immunol*, 11(3), 163-75 (2011)
DOI: 10.1038/nri2957

97. L. Philippe, G. Alsaleh, G. Suffert, A. Meyer, P. Georgel, J. Sibilia, D. Wachsmann and S. Pfeffer: TLR2 expression is regulated by microRNA miR-19 in rheumatoid fibroblast-like synoviocytes. *J Immunol*, 188(1), 454-61 (2012)
DOI: 10.4049/jimmunol.1102348

98. M. R. Benakanakere, Q. Li, M. A. Eskan, A. V. Singh, J. Zhao, J. C. Galicia, P. Stathopoulou, T. B. Knudsen and D. F. Kinane: Modulation of TLR2 protein expression by miR-105 in human oral keratinocytes. *J Biol Chem*, 284(34), 23107-15 (2009)
DOI: 10.1074/jbc.M109.013862

99. E. M. Quinn, J. H. Wang, G. O'Callaghan and H. P. Redmond: MicroRNA-146a is upregulated by and negatively regulates TLR2 signaling. *PLoS One*, 8(4), e62232 (2013)
DOI: 10.1371/journal.pone.0062232

100. H. Guo, Y. Chen, X. Hu, G. Qian, S. Ge and J. Zhang: The regulation of Toll-like receptor 2 by miR-143 suppresses the invasion and migration of a subset of human colorectal carcinoma cells. *Mol Cancer*, 12, 77 (2013)
DOI: 10.1186/1476-4598-12-77

101. Y. Liu, Y. Wang, M. Yamakuchi, S. Isowaki, E. Nagata, Y. Kanmura, I. Kitajima and I. Maruyama: Upregulation of toll-like receptor 2 gene expression in macrophage response to peptidoglycan and high concentration of lipopolysaccharide is involved in NF-kappa b activation. *Infect Immun*, 69(5), 2788-96 (2001)

DOI: 10.1128/IAI.69.5.2788-2796.2001

102. T. Matsuguchi, T. Musikacharoen, T. Ogawa and Y. Yoshikai: Gene expressions of Toll-like receptor 2, but not Toll-like receptor 4, is induced by LPS and inflammatory cytokines in mouse macrophages. *J Immunol*, 165(10), 5767-72 (2000)
DOI: 10.4049/jimmunol.165.10.5767

103. L. Chavez-Sanchez, M. G. Garza-Reyes, J. E. Espinosa-Luna, K. Chavez-Rueda, M. V. Legorreta-Haquet and F. Blanco-Favela: The role of TLR2, TLR4 and CD36 in macrophage activation and foam cell formation in response to oxLDL in humans. *Hum Immunol*, 75(4), 322-9 (2014)
DOI: 10.1016/j.humimm.2014.01.012

104. J. P. Bras, A. M. Silva, G. A. Calin, M. A. Barbosa, S. G. Santos and M. I. Almeida: miR-195 inhibits macrophages pro-inflammatory profile and impacts the crosstalk with smooth muscle cells. *PLoS One*, 12(11), e0188530 (2017)
DOI: 10.1371/journal.pone.0188530

105. D. S. O'Mahony, U. Pham, R. Iyer, T. R. Hawn and W. C. Liles: Differential constitutive and cytokine-modulated expression of human Toll-like receptors in primary neutrophils, monocytes, and macrophages. *Int J Med Sci*, 5(1), 1-8 (2008)
DOI: 10.7150/ijms.5.1

106. L. Meng, W. Zhu, C. Jiang, X. He, W. Hou, F. Zheng, R. Holmdahl and S. Lu: Toll-like receptor 3 upregulation in macrophages participates in the initiation and maintenance of pristane-induced arthritis in rats. *Arthritis Res Ther*, 12(3), R103 (2010)
DOI: 10.1186/ar3034

107. C. Jiang, W. Zhu, J. Xu, B. Wang, W. Hou, R. Zhang, N. Zhong, Q. Ning, Y. Han, H. Yu, J. Sun, L. Meng and S. Lu: MicroRNA-26a negatively regulates toll-like receptor 3 expression of rat macrophages and ameliorates pristane induced arthritis in rats. *Arthritis Res Ther*, 16(1), R9 (2014)
DOI: 10.1186/ar4435

108. X. Hu, J. Ye, A. Qin, H. Zou, H. Shao and K. Qian: Both MicroRNA-155 and Virus-Encoded MiR-155 Ortholog Regulate TLR3 Expression. *PLoS One*, 10(5), e0126012 (2015)
DOI: 10.1371/journal.pone.0126012

109. J. B. Johnnidis, M. H. Harris, R. T. Wheeler, S. Stehling-Sun, M. H. Lam, O. Kirak, T. R. Brummelkamp, M. D. Fleming and F. D. Camargo: Regulation of progenitor cell proliferation and granulocyte function by microRNA-223. *Nature*, 451(7182), 1125-9 (2008)
DOI: 10.1038/nature06607

110. X. M. Chen, P. L. Splinter, S. P. O'Hara and N. F. LaRusso: A cellular micro-RNA, let-7i, regulates Toll-like receptor 4 expression and contributes to cholangiocyte immune responses against Cryptosporidium parvum infection. *J Biol Chem*, 282(39), 28929-38 (2007)
DOI: 10.1074/jbc.M702633200

111. G. Hu, A. Y. Gong, A. L. Roth, B. Q. Huang, H. D. Ward, G. Zhu, N. F. Larusso, N. D. Hanson and X. M. Chen: Release of luminal exosomes contributes to TLR4-mediated epithelial antimicrobial defense. *PLoS Pathog*, 9(4), e1003261 (2013)
DOI: 10.1371/journal.ppat.1003261

112. G. Hu, R. Zhou, J. Liu, A. Y. Gong, A. N. Eischeid, J. W. Dittman and X. M. Chen: MicroRNA-98 and let-7 confer cholangiocyte expression of cytokine-inducible Src homology 2-containing protein in response to microbial challenge. *J Immunol*, 183(3), 1617-24 (2009)
DOI: 10.4049/jimmunol.0804362

113. A. Androulidaki, D. Iliopoulos, A. Arranz, C. Doxaki, S. Schworer, V. Zacharioudaki, A. N. Margioris, P. N. Tsichlis and C. Tsatsanis: The kinase Akt1 controls macrophage response to lipopolysaccharide by regulating microRNAs. *Immunity*, 31(2), 220-31 (2009)
DOI: 10.1016/j.immuni.2009.06.024

114. J. Wu, P. Niu, Y. Zhao, Y. Cheng, W. Chen, L. Lin, J. Lu, X. Cheng and Z. Xu: Impact of miR-223-3p and miR-2909 on inflammatory factors IL-6, IL-1ss, and TNF-alpha, and the TLR4/TLR2/NF-kappaB/STAT3 signaling pathway induced by lipopolysaccharide in human adipose stem cells. *PLoS One*, 14(2), e0212063 (2019)
DOI: 10.1371/journal.pone.0212063

115. Y. Yan, K. Lu, T. Ye and Z. Zhang: MicroRNA223 attenuates LPSinduced inflammation in an acute lung injury model via the NLRP3 inflammasome and TLR4/NFkappaB signaling pathway via RHOB. *Int J Mol Med*, 43(3), 1467-1477 (2019)
DOI: 10.3892/ijmm.2019.4075

116. K. Yang, Y. S. He, X. Q. Wang, L. Lu, Q. J. Chen, J. Liu, Z. Sun and W. F. Shen: MiR-146a inhibits oxidized low-density lipoprotein-induced lipid accumulation and inflammatory response via targeting toll-like receptor 4. *FEBS Lett*, 585(6), 854-60 (2011)
DOI: 10.1016/j.febslet.2011.02.009

117. W. Liu, Y. H. Wu, L. Zhang, B. Xue, Y. Wang, B. Liu, X. Y. Liu, F. Zuo, X. Y. Yang, F. Y. Chen, R. Duan, Y. Cai, B. Zhang and Y. Ji: MicroRNA-146a suppresses rheumatoid arthritis fibroblast-like synoviocytes proliferation and inflammatory responses by inhibiting the TLR4/NF-kB signaling. *Oncotarget*, 9(35), 23944-23959 (2018)
DOI: 10.18632/oncotarget.24050

118. K. D. Taganov, M. P. Boldin, K. J. Chang and D. Baltimore: 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*, 103(33), 12481-6 (2006)
DOI: 10.1073/pnas.0605298103

119. L. Tserel, T. Runnel, K. Kisand, M. Pihlap, L. Bakhoff, R. Kolde, H. Peterson, J. Vilo, P. Peterson and A. Rebane: MicroRNA expression profiles of human blood monocyte-derived dendritic cells and macrophages reveal miR-511 as putative positive regulator of Toll-like receptor 4. *J Biol Chem*, 286(30), 26487-95 (2011)
DOI: 10.1074/jbc.M110.213561

120. F. J. Sheedy, E. Palsson-McDermott, E. J. Hennessy, C. Martin, J. J. O'Leary, Q. Ruan, D. S. Johnson, Y. Chen and L. A. O'Neill: Negative regulation of TLR4 via targeting of the proinflammatory tumor suppressor PDCD4 by the microRNA miR-21. *Nat Immunol*, 11(2), 141-7 (2010)
DOI: 10.1038/ni.1828

121. X. Zhang, C. Wang, S. Shan, X. Liu, Z. Jiang and T. Ren: TLR4/ROS/miRNA-21

pathway underlies lipopolysaccharide instructed primary tumor outgrowth in lung cancer patients. *Oncotarget*, 7(27), 42172-42182 (2016)
DOI: 10.18632/oncotarget.9902

122. Z. Xu, M. Sharma, A. Gelman, R. Hachem and T. Mohanakumar: Significant role for microRNA-21 affecting toll-like receptor pathway in primary graft dysfunction after human lung transplantation. *J Heart Lung Transplant*, 36(3), 331-339 (2017)
DOI: 10.1016/j.healun.2016.08.028

123. S. R. Aungier, H. Ohmori, M. Clinton and N. A. Mabbott: MicroRNA-100-5p indirectly modulates the expression of Il6, Ptgs1/2 and Tlr4 mRNA in the mouse follicular dendritic cell-like cell line, FL-Y. *Immunology*, 144(1), 34-44 (2015)
DOI: 10.1111/imm.12342

124. K. M. Akat, Y. A. Lee, A. Hurley, P. Morozov, K. E. Max, M. Brown, K. Bogardus, A. Sopeyin, K. Hildner, T. G. Diacovo, M. F. Neurath, M. Borggrefe and T. Tuschl: Detection of circulating extracellular mRNAs by modified small-RNA-sequencing analysis. *JCI Insight*, 5 (2019)
DOI: 10.1172/jci.insight.127317

125. M. Arenas-Padilla and V. Mata-Haro: Regulation of TLR signaling pathways by microRNAs: implications in inflammatory diseases. *Cent Eur J Immunol*, 43(4), 482-489 (2018)
DOI: 10.5114/ceji.2018.81351

126. H. Rupani, R. T. Martinez-Nunez, P. Dennison, L. C. Lau, N. Jayasekera, T. Havelock, A. S. Francisco-Garcia, C. Grainge, P. H. Howarth and T. Sanchez-Elsner: Toll-like Receptor 7 Is Reduced in Severe Asthma and Linked to an Altered MicroRNA Profile. *Am J Respir Crit Care Med*, 194(1), 26-37 (2016)
DOI: 10.1164/rccm.201502-0280OC

127. Z. Huang, J. Gan, Z. Long, G. Guo, X. Shi, C. Wang, Y. Zang, Z. Ding, J. Chen, J. Zhang and L. Dong: Targeted delivery of let-7b to reprogramme tumor-associated macrophages and tumor infiltrating dendritic cells for tumor rejection. *Biomaterials*, 90, 72-84 (2016)
DOI: 10.1016/j.biomaterials.2016.03.009

128. W. A. He, F. Calore, P. Londhe, A. Canella, D. C. Guttridge and C. M. Croce: Microvesicles containing miRNAs promote muscle cell death in cancer cachexia via TLR7. *Proc Natl Acad Sci U S A*, 111(12), 4525-9 (2014)
DOI: 10.1073/pnas.1402714111

129. P. Ranganathan, A. Ngankeu, N. C. Zitzer, P. Leoncini, X. Yu, L. Casadei, K. Challagundla, D. K. Reichenbach, S. Garman, A. S. Ruppert, S. Volinia, J. Hofstetter, Y. A. Efebera, S. M. Devine, B. R. Blazar, M. Fabbri and R. Garzon: Serum miR-29a Is Upregulated in Acute Graft-versus-Host Disease and Activates Dendritic Cells through TLR Binding. *J Immunol*, 198(6), 2500-2512 (2017)
DOI: 10.4049/jimmunol.1601778

130. N. Hoshikawa, A. Sakai, S. Takai and H. Suzuki: Targeting Extracellular miR-21-TLR7 Signaling Provides Long-Lasting Analgesia in Osteoarthritis. *Mol Ther Nucleic Acids*, 19, 199-207 (2020)
DOI: 10.1016/j.omtn.2019.11.011

131. C. K. Park, Z. Z. Xu, T. Berta, Q. Han, G. Chen, X. J. Liu and R. R. Ji: Extracellular microRNAs activate nociceptor neurons to elicit pain via TLR7 and TRPA1. *Neuron*, 82(1), 47-54 (2014)
DOI: 10.1016/j.neuron.2014.02.011

132. F. Heil, H. Hemmi, H. Hochrein, F. Ampenberger, C. Kirschning, S. Akira, G. Lipford, H. Wagner and S. Bauer: Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. *Science*, 303(5663), 1526-9 (2004)
DOI: 10.1126/science.1093620

133. V. Hornung, M. Guenthner-Biller, C. Bourquin, A. Ablasser, M. Schlee, S. Uematsu, A. Noronha, M. Manoharan, S. Akira, A. de Fougerolles, S. Endres and G. Hartmann: Sequence-specific potent induction of IFN-alpha by short interfering RNA in plasmacytoid dendritic cells through TLR7. *Nat Med*, 11(3), 263-70 (2005)
DOI: 10.1038/nm1191

134. M. Sioud: Induction of inflammatory cytokines and interferon responses by double-stranded and single-stranded siRNAs is sequence-dependent and requires endosomal localization. *J Mol Biol*, 348(5), 1079-90 (2005)
DOI: 10.1016/j.jmb.2005.03.013

135. A. Forsbach, J. G. Nemorin, C. Montino, C. Muller, U. Samulowitz, A. P. Vicari, M. Jurk, G. K. Mutwiri, A. M. Krieg, G. B. Lipford and J. Vollmer: Identification of RNA sequence motifs stimulating sequence-specific TLR8-dependent immune responses. *J Immunol*, 180(6), 3729-38 (2008)
DOI: 10.4049/jimmunol.180.6.3729

136. S. S. Diebold, C. Massacrier, S. Akira, C. Paturel, Y. Morel and C. Reis e Sousa: Nucleic acid agonists for Toll-like receptor 7 are defined by the presence of uridine ribonucleotides. *Eur J Immunol*, 36(12), 3256-67 (2006)
DOI: 10.1002/eji.200636617

137. A. D. Judge, V. Sood, J. R. Shaw, D. Fang, K. McClintock and I. MacLachlan: Sequence-dependent stimulation of the mammalian innate immune response by synthetic siRNA. *Nat Biotechnol*, 23(4), 457-62 (2005)
DOI: 10.1038/nbt1081

138. H. Peacock, R. V. Fucini, P. Jayalath, J. M. Ibarra-Soza, H. J. Haringsma, W. M. Flanagan, A. Willingham and P. A. Beal: Nucleobase and ribose modifications control immunostimulation by a microRNA-122-mimetic RNA. *J Am Chem Soc*, 133(24), 9200-3 (2011)
DOI: 10.1021/ja202492e

139. M. de Marcken, K. Dhaliwal, A. C. Danielsen, A. S. Gautron and M. Dominguez-Villar: TLR7 and TLR8 activate distinct pathways in monocytes during RNA virus infection. *Sci Signal*, 12(605) (2019)
DOI: 10.1126/scisignal.aaw1347

140. D. E. Giza, E. Fuentes-Mattei, M. D. Bullock, S. Tudor, M. J. Goblirsch, M. Fabbri, F. Lupu, S. J. Yeung, C. Vasilescu and G. A. Calin: Cellular and viral microRNAs in sepsis: mechanisms of action and clinical applications. *Cell Death Differ*, 23(12), 1906-1918 (2016)
DOI: 10.1038/cdd.2016.94

141. S. Tudor, D. E. Giza, H. Y. Lin, L. Fabris, K. Yoshiaki, L. D'Abundo, K. M. Toale, M. Shimizu, M. Ferracin, K. B. Challagundla, M. A. Cortez, E. Fuentes-Mattei, D. Tulbure, C. Gonzalez, J. Henderson, M. Row, T. W. Rice, C. Ivan, M. Negrini, M. Fabbri, J. S. Morris, S. C. Yeung, C. Vasilescu and G. A. Calin: Cellular and Kaposi's sarcoma-associated herpes virus microRNAs in sepsis and surgical trauma. *Cell Death Dis*, 5, e1559 (2014)

DOI: 10.1038/cddis.2014.515

142. L. S. Young and A. B. Rickinson: Epstein-Barr virus: 40 years on. *Nat Rev Cancer*, 4(10), 757-68 (2004)
DOI: 10.1038/nrc1452

143. A. Ferrajoli, C. Ivan, M. Ciccone, M. Shimizu, Y. Kita, M. Ohtsuka, L. D'Abundo, J. Qiang, S. Lerner, N. Nouraee, K. G. Rabe, L. Z. Rassenti, K. Van Roosbroeck, J. T. Manning, Y. Yuan, X. Zhang, T. D. Shanafelt, W. G. Wierda, S. Sabbioni, J. J. Tarrand, Z. Estrov, M. Radovich, H. Liang, M. Negrini, T. J. Kipps, N. E. Kay, M. Keating and G. A. Calin: Epstein-Barr Virus MicroRNAs are Expressed in Patients with Chronic Lymphocytic Leukemia and Correlate with Overall Survival. *EBioMedicine*, 2(6), 572-82 (2015)
DOI: 10.1016/j.ebiom.2015.04.018

144. K. Van Roosbroeck and G. A. Calin: When kissing (disease) counts. *Blood*, 127(16), 1947-8 (2016)
DOI: 10.1182/blood-2016-01-692087

145. T. J. Cremer, D. H. Ravneberg, C. D. Clay, M. G. Piper-Hunter, C. B. Marsh, T. S. Elton, J. S. Gunn, A. Amer, T. D. Kanneganti, L. S. Schlesinger, J. P. Butchar and S. Tridandapani: MiR-155 induction by F. novicida but not the virulent F. tularensis results in SHIP down-regulation and enhanced pro-inflammatory cytokine response. *PLoS One*, 4(12), e8508 (2009)
DOI: 10.1371/journal.pone.0008508

146. R. O. Eren, M. Reverte, M. Rossi, M. A. Hartley, P. Castiglioni, F. Prevel, R. Martin, C. Desponds, L. F. Lye, S. K. Drexler, W. Reith, S. M. Beverley, C. Ronet and N. Fasel: Mammalian Innate Immune Response to a Leishmania-Resident RNA Virus Increases Macrophage Survival to Promote Parasite Persistence. *Cell Host Microbe*, 20(3), 318-328 (2016)
DOI: 10.1016/j.chom.2016.08.001

147. C. E. McCoy, F. J. Sheedy, J. E. Qualls, S. L. Doyle, S. R. Quinn, P. J. Murray and L. A. O'Neill: IL-10 inhibits miR-155 induction by toll-like receptors. *J Biol Chem*, 285(27), 20492-8 (2010)
DOI: 10.1074/jbc.M110.102111

148. H. Zhou, X. Huang, H. Cui, X. Luo, Y. Tang, S. Chen, L. Wu and N. Shen: miR-155 and its star-form partner miR-155* cooperatively regulate type I interferon production by human plasmacytoid dendritic cells. *Blood*, 116(26), 5885-94 (2010)
DOI: 10.1182/blood-2010-04-280156

149. M. Jiang, R. Broering, M. Trippler, J. Wu, E. Zhang, X. Zhang, G. Gerken, M. Lu and J. F. Schlaak: MicroRNA-155 controls Toll-like receptor 3- and hepatitis C virus-induced immune responses in the liver. *J Viral Hepat*, 21(2), 99-110 (2014)
DOI: 10.1111/jvh.12126

150. S. R. Quinn, N. E. Mangan, B. E. Caffrey, M. P. Gantier, B. R. Williams, P. J. Hertzog, C. E. McCoy and L. A. O'Neill: The role of Ets2 transcription factor in the induction of microRNA-155 (miR-155) by lipopolysaccharide and its targeting by interleukin-10. *J Biol Chem*, 289(7), 4316-25 (2014)
DOI: 10.1074/jbc.M113.522730

151. R. M. O'Connell, K. D. Taganov, M. P. Boldin, G. Cheng and D. Baltimore: MicroRNA-155 is induced during the macrophage inflammatory response. *Proc Natl Acad Sci U S A*, 104(5), 1604-9 (2007)

DOI: 10.1073/pnas.0610731104

152. K. Migita, N. Iwanaga, Y. Izumi, C. Kawahara, K. Kumagai, T. Nakamura, T. Koga and A. Kawakami: TNF-alpha-induced miR-155 regulates IL-6 signaling in rheumatoid synovial fibroblasts. *BMC Res Notes*, 10(1), 403 (2017)
DOI: 10.1186/s13104-017-2715-5

153. D. Yee, K. M. Shah, M. C. Coles, T. V. Sharp and D. Lagos: MicroRNA-155 induction via TNF-alpha and IFN-gamma suppresses expression of programmed death ligand-1 (PD-L1) in human primary cells. *J Biol Chem*, 292(50), 20683-20693 (2017)
DOI: 10.1074/jbc.M117.809053

154. H. Li, X. Zhang, L. Gao, J. Min, Y. Zhang, R. Zhang and Y. Yang: TNF-alpha is upregulated in subacute thyroiditis and stimulates expression of miR-155-5p in thyroid follicle cells. *Discov Med*, 26(142), 67-77 (2018)

155. T. Wu, M. Xie, X. Wang, X. Jiang, J. Li and H. Huang: miR-155 modulates TNF-alpha-inhibited osteogenic differentiation by targeting SOCS1 expression. *Bone*, 51(3), 498-505 (2012)
DOI: 10.1016/j.bone.2012.05.013

156. Y. Sun, J. Cai, F. Ma, P. Lu, H. Huang and J. Zhou: miR-155 mediates suppressive effect of progesterone on TLR3, TLR4-triggered immune response. *Immunol Lett*, 146(1-2), 25-30 (2012)
DOI: 10.1016/j.imlet.2012.04.007

157. R. Rao, S. A. Rieder, P. Nagarkatti and M. Nagarkatti: Staphylococcal enterotoxin B-induced microRNA-155 targets SOCS1 to promote acute inflammatory lung injury. *Infect Immun*, 82(7), 2971-9 (2014)
DOI: 10.1128/IAI.01666-14

158. N. J. Galbraith, J. Burton, M. B. Ekman, J. Kenney, S. P. Walker, S. Manek, C. Bishop, J. V. Carter, S. A. Gardner and H. C. Polk: IkappaK-16 decreases miRNA-155 expression and attenuates the human monocyte inflammatory response. *PLoS One*, 12(9), e0183987 (2017)
DOI: 10.1371/journal.pone.0183987

159. A. T. Billeter, J. Hellmann, H. Roberts, D. Druen, S. A. Gardner, H. Sarojini, S. Galandiuk, S. Chien, A. Bhatnagar, M. Spite and H. C. Polk, Jr.: MicroRNA-155 potentiates the inflammatory response in hypothermia by suppressing IL-10 production. *FASEB J*, 28(12), 5322-36 (2014)
DOI: 10.1096/fj.14-258335

160. Y. Wen, X. Zhang, L. Dong, J. Zhao, C. Zhang and C. Zhu: Acetylbritannilactone Modulates MicroRNA-155-Mediated Inflammatory Response in Ischemic Cerebral Tissues. *Mol Med*, 21, 197-209 (2015)
DOI: 10.2119/molmed.2014.00199

161. G. Swaminathan, F. Rossi, L. J. Sierra, A. Gupta, S. Navas-Martin and J. Martin-Garcia: A role for microRNA-155 modulation in the anti-HIV-1 effects of Toll-like receptor 3 stimulation in macrophages. *PLoS Pathog*, 8(9), e1002937 (2012)
DOI: 10.1371/journal.ppat.1002937

162. Z. Wen, L. Xu, X. Chen, W. Xu, Z. Yin, X. Gao and S. Xiong: Autoantibody induction by DNA-containing immune complexes requires HMGB1 with the TLR2/microRNA-155 pathway. *J Immunol*, 190(11), 5411-22 (2013)
DOI: 10.4049/jimmunol.1203301

163. K. Wang and P. F. Li: Foxo3a regulates apoptosis by negatively targeting miR-21. *J Biol Chem*, 285(22), 16958-66 (2010) DOI: 10.1074/jbc.M109.093005

164. B. Gan, C. Lim, G. Chu, S. Hua, Z. Ding, M. Collins, J. Hu, S. Jiang, E. Fletcher-Sananikone, L. Zhuang, M. Chang, H. Zheng, Y. A. Wang, D. J. Kwiatkowski, W. G. Kaelin, Jr., S. Signoretti and R. A. DePinho: FoxOs enforce a progression checkpoint to constrain mTORC1-activated renal tumorigenesis. *Cancer Cell*, 18(5), 472-84 (2010) DOI: 10.1016/j.ccr.2010.10.019

165. T. La, G. Z. Liu, M. Farrelly, N. Cole, Y. C. Feng, Y. Y. Zhang, S. K. Sherwin, H. Yari, H. Tabatabaee, X. G. Yan, S. T. Guo, T. Liu, R. F. Thorne, L. Jin and X. D. Zhang: A p53-Responsive miRNA Network Promotes Cancer Cell Quiescence. *Cancer Res*, 78(23), 6666-6679 (2018) DOI: 10.1158/0008-5472.CAN-18-1886

166. R. Echavarria, D. Mayaki, J. C. Neel, S. Harel, V. Sanchez and S. N. Hussain: Angiopoietin-1 inhibits toll-like receptor 4 signalling in cultured endothelial cells: role of miR-146b-5p. *Cardiovasc Res*, 106(3), 465-77 (2015) DOI: 10.1093/cvr/cvv120

Abbreviations: AP1: activator protein-1; AGO: argonaute; BLP: bacterial lipoprotein; CSF: cerebrospinal fluid; DAMPs: damage-associated molecular patterns; DGCR8: Drosha and the DiGeorge critical region 8 protein; HBV: hepatitis B virus; IL: interleukin; IRAK-1: interleukin-1 receptor-associated kinase 1; LRR: leucine-rich repeat region; LPS: lipopolysaccharide; MMP3: matrix metalloproteinase 3; miRNAs: MicroRNAs; miRISC: miRNA-induced silencing complex; MAPK: mitogen-associated protein kinase; MyD88: Myeloid differentiation primary response gene 88; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PAMPs: pathogen-associated molecular patterns; pri-miRNAs: primary miRNAs; RA: rheumatoid arthritis; SHIP1: Src homology 2 domain-containing inositol polyphosphate-5-phosphatase 1; SARM: Sterile α- and armadillo-motif-containing protein; SLE: systemic lupus erythematosus; TH1: T helper 1; TIRAP or MAL: TIR domain-containing adaptor protein; TRIF: TIR domain-containing adaptor protein inducing IFN-β; TIR: Toll/Interleukin-1 (IL-1) receptor; TLRs: Toll-like receptors; TRAM: TRIF-related adaptor molecule; TNF-α: tumor necrosis factor-alpha; TAMs: tumor-associated macrophages; TIDCs: tumor-infiltrating dendritic cells; UTR: untranslated region.

Key Words: miRNA, TLR, Immunity, Cytokine, SNAP, Chemokine, Review,

Send correspondence to: Indrajit Chowdhury, Department of Obstetrics and Gynecology, Morehouse School of Medicine, 720 Westview Drive Southwest, Atlanta, GA 30310, Tel.: 404-752-1587, Fax: 404-752-1754, E-mail: indrajitfbs@gmail.com