Roles of macrophage polarization and macrophage-derived miRNAs in pulmonary fibrosis

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Supplementary Material

Supplementary Table S1: miRNAs involved in alveolar macrophage polarization and their functions in pulmonary fibrosis

Macrophage derived microRNAs	**Model**	**Targets**	**Potential immune function**	**Reference**
I. Macrophage M1				
↑ miR-21	Mouse	STAT3	Drives M1 and inhibits M2 macrophage polarization	(1)
	BMSCs	TNFα	Inhibit M1 polarization. Low miR-21 levels suggest higher RILI incidence and grade, lower pulmonary function in patients, and enhancement of IL6 and TNFα expressions, especially during the acute phase	(2)
↑ miR-21-5p	Mouse lung I/R model and in vitro H/R model, MSC-Exo	PTEN and PDCD4	Reduced M1 macrophages polarization, lung edema and dysfunction, as well as secretion of HMGB1, IL8, IL1β, IL6, IL17 and TNFα	(3)
↑ miR-33	Mouse	ABCA1 and ABCG1	Elevated proinflammatory cytokines, suppression of anti-inflammatory lipid transporters	(4)
↑ miR-34a	Mouse	*Notch1*	Inhibits production of pro-inflammatory cytokines	(5)
↑ miR-101	Human THP-1-derived macrophages and HepG2 hepatoblastoma cell line	ABCA1	Pro-inflammatory miR-101 negatively regulate the expression of ABCA1 under inflammatory conditions such as IL6 and TNFα	(6)
	Mouse macrophage RAW264.7 cell line	MKP-1	Enhanced LPS-induced pro-inflammatory cytokine production in macrophages via activation of MAPK by targeting MAPK phosphatase-1	(7)
↑ miR-125b-5p	Mouse BMDMs	Not reported	Inhibition of miR-125b-5p mitigates M1 macrophage polarization	(8)
↑ miR-125b	Mouse	IRF4	Enhance pro-inflammatory responses, induced immune responses with increased Ag-specific T cell activation and antitumor immunity	(9)
↑ miR-127-3p	Mouse BMDMs	Not reported	MiR-127-3p promotes M1 signature gene expression	(8)

↑ miR-127	Mouse	Bcl6 and DUSP1	Increased production of proinflammatory cytokines, promote proinflammatory M1 macrophage development through JNK-dependent mechanism	(10)
↑ miR-140	Mouse lung fibroblasts	TGFβ1/Smad3 pathway	Inhibits fibronectin in lung fibroblasts	(11)
↑ miR-146b	Mouse BMDMs	TLR4, MyD88, IRAK1, TRAF6	Anti-inflammatory activity, modulates TLR4 signaling pathway, miR-146b overexpression ameliorates LPS-induced ALI	(12, 13)
↑ miR-148a-3p	Mouse	*Pten*	A novel downstream molecule of Notch signaling to promote the differentiation of monocytes into macrophages in the presence of GM-CSF, enhance M1 macrophage polarization and pro-inflammatory responses through PTEN/AKT-mediated upregulation of NFκB signaling	(14)
↑ miR-155	Mouse	SHIP-1	Significantly reduced fibrosis and EMT in miR-155KO mice involving PI3K/AKT, JAK/STAT3, and SMAD/STAT signaling pathways	(15)
	Mouse and lung fibroblasts	*LXRα*	Reduced exacerbated fibrotic response, profibrotic IPF phenotype and fibroblasts	(16)
	Mouse	SOCS-1	Promote LPS-induced ALI in mice and rats	(17)
	Mouse	IL13Rα1	Development of a healthy immune system and functions as well as in the inflammatory pro-Th1/M1 immune profile	(18)
↑ miR-200b	Mouse	DUSP1	Promotes LPS-induced pro-inflammatory cytokines and injury, pro-inflammatory activities	(19)
↑ miR-200c	Mouse	DUSP1	Promotes LPS-induced pro-inflammatory cytokines and injury, pro-inflammatory activities	(19)
↑ miR-342-5p	Mouse	Bmpr2, Akt1	Induces pro-inflammatory macrophage markers (NOS2 and IL6) in the formation of atherosclerotic lesions	(20)
↑ miR-429	Mouse	DUSP1	Promotes LPS-induced pro-inflammatory cytokines and ALI	(19)
↓ let-7e	Mouse BMDM	MK2	Downregulated let-7e promoted LPS-induced macrophage activation and ALI via MK2 and enhanced CREB activation. The let-7e level is negatively associated with the LPS-induced	(21)

			expression of proinflammatory cytokines TNF-α and IL6, as well as chemokine MIP-2.	
II. Macrophage M2 (M2a, M2b, M2c and M2d subpopulations)				
↑ let-7c	Mouse	STAT3	Anti-inflammatory with inhibition of cytokines TNFα, IL6 and IL1β in LPS treated alveolar macrophages by targeting STAT3	(22)
	Mouse	PAK1	EZH2/let-7c/PAK1 axis promotes inflammatory macrophage M1 polarization via NIK-IKK-NF-κB signaling	(23)
	Mouse	C/EBP-δ	Overexpression of let-7c in GM-BMM diminished M1 phenotype expression while promoting polarization to the M2 phenotype	(24)
↑ miR-27a-3p	MSC-EVs	NFKB1	Induced M2 macrophage polarization. MSC-EVs derived miR-27a-3p alleviate ALI and M2 macrophage polarization.	(25)
↑ miR-101*	Mouse and human lung fibroblasts (in vitro)	FZD4, FZD6, and TGFBR1	Mir-101 mitigate pulmonary fibrosis by inhibiting fibroblast proliferation and differentiation via supressing WNT5a/NFATc2 and TGF-/Smad2/3 pathways	(26)
↑ miR-124	Mouse	RELA/p65	Overexpression of miR-124-3p in NC8383 cells and lung tissues significantly suppressed LPS-induced p65 expression and cell apoptosis	(27)
	Mouse	MCP-1	Promotes M2 macrophage polarization, high miR-124 level in lungs prevent LPS-induced myeloperoxidase activity mitigating ALI	(28)
	Mouse and macrophage cell line RAW264.7	STAT3 and TACE	Key mediator for the cholinergic anti-inflammatory action	(29)
	Mouse and macrophage cell line RAW264.7	C/EBPα	M2 phenotype development and maintenance	(30)
↑ miR-125a-5p	Mouse GM-BMM and M-BMM	TNFα	Promotes M2 and suppresses M1 macrophage polarization. Significantly enhance the ability of GM-BMM to ingest apoptotic cells	(31)
↑ miR-135b	Mouse	MAPK6	Downregulation of pro-inflammatory factors and cartilage damage, induces M2 polarization of synovial macrophages	(32)
↑ miR-146a	Mouse	TRAF6, IRAK1 and IRF5	Anti-inflammatory targeting TLR4 signaling, protects from ALI via M2 macrophage activation	(33)

↑ miR-328	Mouse	FAM13A	Progression of pulmonary fibrosis	(34)
↑ miR-511-3p	Human monocytes - primary cells and cell lines	TLR4	Mediates anti-inflammatory cytokines production of TGFβ and glucocorticoids in endotoxin tolerant monocytes	(35)
	CRE-induced mouse model of asthma	Ccl2	Polarizes macrophages toward the M2 phenotype	(36)
↑ miR-378-3p	Mouse and RAW264.7 cells	IL-4R/PI3K/Akt-signaling pathway	Alternative macrophage activation	(37)
↑ miR-223	Mouse	HIF-1α, PDK-1 and PFK	Anti-inflammatory, prevent conversion into M1 macrophage polarization after LPS stimulation	(38)
	Mouse	STAT3	Promotes anti-inflammatory response	(39)
↓ let-7a	Human, mouse, BMDM and lung fibroblasts (in vitro)	c-Myc	Arsenite-induced M2 polarization of macrophages	(40)
↓ miR-29a	In vitro macrophage cell culture model of PMA activated THP1 cells	Not reported	Mir-29a downregulation displayed a profibrotic profile with activation of collagen 1a pathway in BAL alveolar macrophages from IPF patients	(41)
↓ miR-33	Mouse	AMPK-α and PGC-1α	Mir-33 deficiency may be protective against bleomycin induced lung injury and fibrosis	(42, 43)
↓ miR-34a	Mouse	Klf4	Inhibition of miRNA-34a promotes M2 macrophage polarization and improves LPS-induced lung injury	(44)
↓ miR-127	Mouse	Bcl6 and Dusp1	Deletion of miR-127 impaired M1 gene expression and led to a M2-biased response	(10)
↓ miR-140	Mouse	Fibronectin, α-SMA and Smad3	Loss of miR-140 showed increased TGF-β1 signaling myofibroblast in lung fibroblasts. miR-140 is a key protective molecule against RILF through inhibiting myofibroblast differentiation and inflammation	(11)
↓ miR-155	Mouse and IPF lung fibroblasts (in vitro)	*ZNF652*	Increased collagen and TGF-β production,	(16)

	Mouse	IL13Rα1	MiR-155 affects the IL-13-dependent regulation of SOCS1, DC-SIGN, CCL18, CD23, and SERPINE involved in the establishment of M2/pro-Th2 phenotype in macrophages	(18)
↓ miR-185	In vitro macrophage cell culture model of PMA activated THP1 cells	Not reported	MiR-185 downregulation displayed a profibrotic profile with activation of AKT pathway in BAL alveolar macrophages from IPF patients	(41)
miR-320a*	Human and Mouse	TGFBR2 and IGF1R	Important regulator of fibrotic process in ILD	(45)

*Not investigated for macrophage M1/M2 polarization

Abbreviations: ABCA1, ATP-binding cassette transporter A1; Akt1, AKT serine/threonine kinase 1; ALI, acute lung injury; AMPK-α, protein kinase AMP-activated catalytic subunit alpha; Bcl6, BCL6 transcription repressor; BAL, bronchoalveolar lavage fluid; BMDMs/BMM, bone marrow derived macrophages; Bmpr2, bone morphogenetic protein receptor type 2; BMSCs, bone marrow mesenchymal stem cells; C/EBP, CCAAT enhancer binding protein beta; c-Myc, MYC proto-oncogene, bHLH transcription factor; CRE, cockroach extract; DUSP1, dual specificity phosphatase 1; EMT, endothelial-mesenchymal transition; EZH2, enhancer of zeste homolog 2; FAM13A, family with sequence similarity 13 member A; FZD, frizzled class receptor; GM-CSF, granulocyte macrophage colony-stimulating factor; H/R model, hypoxia/reoxygenation model; HIF-1α, hypoxia inducible factor 1 subunit alpha; I/R model, ischemia/reperfusion model; IGF1R, insulin like growth factor 1 receptor l; IL13Rα1, interleukin 13 receptor subunit alpha 1; IPF: Idiopathic pulmonary fibrosis; IRAK1, interleukin 1 receptor associated kinase 1; IRF, interferon regulatory factor 4; KLF4, Kruppel like factor 4; let-7, microRNA lethal-7; LPS, lipopolysaccharide; LXRα, nuclear receptor subfamily 1 group H member 3; MAP, mitogen-activated protein; MAPK, mitogen-activated protein kinase; MAPK6, mitogen-activated protein kinase 6; MCP-1, C-C motif chemokine ligand 2; miR, microRNA; MK2, Mitogen-activated protein kinase (MAPK)-activated protein kinase 2; MKP-1, mitogen-activated protein kinase phosphatase 1; MSC-EVs, Mesenchymal stem cell–derived extracellular vesicles; MyD88, MYD88 innate immune signal transduction adaptor; NFKB1, nuclear factor kappa B subunit 1; Notch1, notch receptor 1; PAK1, p21 (RAC1) activated kinase 1; PAKs, p21-activated kinases; PDCD4, programmed cell death 4; PDK-1, pyruvate dehydrogenase kinase 1; PFK, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PGC-1α, PPARG coactivator 1 alpha; PMA, phorbol 12-myristate 13-acetate; PTEN, phosphatase and tensin homolog; RELA/p65, RELA proto-oncogene, NF-kB subunit; RILF, Radiation-induced lung fibrosis; RILI, radiation-induced lung injury; SHIP-1, inositol polyphosphate-5-phosphatase D; Smad3, SMAD family member 3; SOCS, suppressors of cytokine signaling; SOCS-1, suppressor of cytokine signaling 1; STAT3, signal transducer and activator of transcription 3; TACE, TNF-α converting enzyme; TGFBR, transforming growth factor beta receptor; TGFβ1, transforming growth factor beta 1; TLR, Toll-like receptor; TNF, tumour necrosis factor; TRAF6, TNF receptor associated factor 6; ZNF652, zinc finger protein 652; α-SMA, alpha smooth muscle actin.

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