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Roles of Macrophage Polarization and Macrophage-Derived miRNAs in Pulmonary Fibrosis

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This mini-review summarizes the current evidence for the role of macrophage activation and polarization in inflammation and immune response pertinent to interstitial lung disease, specifically pulmonary fibrosis. In the fibrosing lung, the production and function of inflammatory and fibrogenic mediators involved in the disease development have been reported to be regulated by the effects of polarized M1/M2 macrophage populations. The M1 and M2 macrophage phenotypes were suggested to correspond with the pro-inflammatory and pro-fibrogenic signatures, respectively. These responses towards tissue injury followed by the development and progression of lung fibrosis are further regulated by macrophage-derived microRNAs (miRNAs). Besides cellular miRNAs, extracellular exosomal-miRNAs derived from M2 macrophages have also been proposed to promote the progression of pulmonary fibrosis. In a future perspective, harnessing the noncoding miRNAs with a key role in the macrophage polarization is, therefore, suggested as a promising therapeutic strategy for this debilitating disease.

Keywords: macrophage plasticity, M1/M2 polarization, MicroRNAs, exosomes, pulmonary fibrosis

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INTRODUCTION

Pulmonary fibrosis (PF) is a progressive, irreversible and lethal lung disease and has remained a challenge for clinicians and researchers. The tissue injury accompanied by cellular inflammation in the lungs drives fibrotic response and thus, plays a crucial role in the pathogenesis of fibrosis. Inflammatory cells release TGF-β, the key regulator of several profibrotic cytokines/chemokines, their receptors/subunits, and growth factors inducing epithelial-mesenchymal transition (EMT) (1–3). The pro-inflammatory and profibrotic cytokines involved in PF promote inflammation and irreversible damage to lung architecture with the loss of alveolar-capillary barrier basal membrane leading to persistent fibrosis (4). These pathogenic factors for PF have further been reported as associated with genetic factors including gene variants and non-coding regulatory microRNAs (3–7).

The tissue-resident macrophages (M0) are versatile cells that exhibit a high degree of plasticity represented by classically activated M1 (pro-inflammatory) or alternatively activated M2 (anti-inflammatory/pro-fibrotic) macrophages (8). The macrophage polarization is extremely variable and switching of one "activation-type" to another, stimulated by appropriate factors or tissue

microenvironment, is a rapid and reversible process. The cross-talk between macrophages and the microenvironment regulates tissue regeneration, flagged with key surface markers in both pro-regenerative and profibrotic environments (9).

Thus, besides the development of tissue homeostasis, these cells are suggested with sequential roles in both induction and resolution of inflammation. The M0 macrophages can polarize to M1 or M2 (M2a, M2b, M2c, and M2d) in response to different activators, such as LPS/IFNγ and IL4/IL13, respectively (10). The M1 macrophage phenotype can also be stimulated without the presence of lymphocytes, for example, by inflammatory cytokines and microorganism-derived molecules (10–13). The anti-inflammatory or immune-compromised state associated with the M2 macrophage phenotype is also supported with suppressed multiple interferon-associated pathways as one of the most prominent signals common among all M2-polarizing stimuli (14). The M1 macrophage can readily repolarize to M2a (stimulated with reduced IL10 and TNFα, and increased Ym1 level) and M2b (increased IL10 and reduced TNFα) subpopulations (13). Similarly, macrophage M2b can convert to other M2 subtypes in response to different stimuli (15). The different approaches to macrophage polarization have been associated with both the demerits and benefits influencing their utility for specific tissues. Where possible, future therapeutic approaches are suggested to consider tailoring of strategy towards the formation of a specific tissue-microenvironment, as well as promotion of specific disease-associated cell subsets, to improve efficacy and minimize off-target effect (11).

In deciphering pathomechanisms of lung fibrosis, pulmonary macrophages have been implicated with a key role in the fibrogenic process. The PF has been proposed to be regulated by macrophage plasticity (M1/M2 polarization) with an immunogenic signature network of chemokines such as MCP-1, MIP-1α, CCL18, and cytokines such as TNFα, TGFβ1, and their respective signaling pathways (16–18). The pro-inflammatory M1 macrophage polarization with overexpression of iNOS, TNFα, IL1, IL6, IL12, IL23, MCP-1, and IFNγis associated with inflammation, antitumoral functions and graft rejection (**Table 1**). The anti-inflammatory M2 macrophage polarization, characterised by overexpression of signature proteins such as TGFβ1, IL10, Arginase1, CD204, CD206, VEGF, Ym1, PDGF, MMPs, and IL4Ralpha, was associated with immune regulation, matrix deposition, tissue remodelling, protumoral functions, and graft acceptance (17, 19). The antitumoral and protumoral role of M1 and M2 macrophages, respectively, are further supported with longer survival outcomes among patients with a high M1/M2 ratio in cancers such as ovarian (20, 21) and breast (22) cancer.

ROLE OF LUNG MACROPHAGE POLARIZATION IN PULMONARY FIBROSIS

Macrophages are innate immune cells with antimicrobial phagocytic activity and also play a key role in the pathogenesis of fibrotic disease of pulmonary interstitium. Macrophages are involved at all stages of lung injury and repair, and can promote as well as inhibit fibrosis (16, 23). Airway lumen-based Alveolar macrophages (AM) with surface markers $CD11b^{low}$ $CD11c^{++}$

TABLE 1 | Macrophage subtypes, its activators and implication of cytokines and chemokines in functional response that is also regulated by microRNAs-mediated macrophage plasticity.

M1 and M2 subtypes	Polarization activators	Cytokines and chemokines	Functional response	MicroRNAs expression and its role in M1/M2 macrophage polarization
M1	LPS, IFNγ, TNFα and GM-CSF	Cytokines: TNFα, IL1β, IL6, IL8/CXCL8, IL12, IL23 Chemokines: CCL2, CCL3, CCL4, CCL5, CCL8, CCL9, CCL10, CCL11, CXCL1	Th1 response to infection; produces pro-inflammatory molecules, including TNFα and IL1, IL6, IL12, IL23	↑: miR-21 (M1⊣; M2→), -33 (M1→; M2⊣), -34a (M1→; M2⊣), -101 (M1→; M2⊣), -125b-5p (M1→; M2⊣), -146b (M1⊣), -155 (M1→; M2⊣), -342-5p (M1→) ↓: miR-125b-5p (M1⊣), let-7e (M1⊣)
M2a	IL4, IL13	Cytokines: IL10, TGFβ, IL1Rα Chemokines: CCL17, CCL22, CCL24	Th2 cells, eosinophils, basophils, and macrophages produce IL4. Facilitation of parasite encapsulation	↑: miR-124 (M1⊣; M2→), -125a-5p (M1→), -135b (M2↑), -146a (M1⊣; M2→), let-7c (M1⊣; M2→), -511-3p (M2→), -378-3p (M2→), -223 (M1⊣; M2→), ↓: miR-140 (M2→)
M2b	Immune complexes plus TLR or IL1R ligands	Cytokines: TNF, IL1β, IL6, IL10 Chemokines: CCL1	Immunoregulation with up-regulated IL10 and antigen presentation (MHC II, CD86), and down-regulated IL12	
M2c	IL10, TGFβ1 and glucocorticoids	Cytokines: IL10, TGFβ	Tissue remodelling and extracellular matrix production	
M2d	IL6 and adenosine	–	Tumour-associated immune regulation	

TNF-α, Tumour necrosis factor-α; IFN-γ, Interferon-γ, LPS, lipopolysaccharide; GM-CSF, granulocyte-macrophage colony stimulation factor; IL, interleukin; miR, microRNA.
Symbols for MicroRNA expression level: ↑, up-regulation; ↓, down-regulation.
Symbols for M1/M2 macrophage polarization: →, progression; ⊣, inhibition.

$CD169^+$, and lung parenchymal interstitial macrophages (IM) with $CD11b^+$ $CD11c^{lo}$ $CD169^-$ are the two major distinct macrophage populations contributing to lung homeostasis (24). During the development processes of tissue injury and inflammatory reaction and their subsequent progression to PF, AM and IM are polarized to different cell phenotypes - M1 and M2 macrophages, respectively (16, 25). During tissue damage and the early inflammatory phase, activation of M1 macrophages clears the pathogenic microorganisms and promotes inflammation through extracellular matrix degrading matrix metalloproteases (MMPs) and pro-inflammatory cytokines. The active cytokine milieu, including elevated Th1 cytokines, IL2, IFNγ, and TNFα, is believed to drive the classical pro-inflammatory (M1) macrophage activation, while a proportion of anti-inflammatory M2 macrophages tends to be higher in other types of interstitial lung diseases (ILDs), including idiopathic pulmonary fibrosis (IPF) (26).

The enhanced M2 macrophage polarization has been suggested to inhibit the inflammatory reaction and/or directly regulate the development and progression of fibrotic lung diseases through the production of chemokines, MMPs, tissue inhibitor of metalloproteinases (TIMPs), and fibronectin as well as, the capability of M2 to differentiate into fibrocyte-like cells that express collagen (27–30). Among ILDs, an increased proportion of M2 macrophages has been observed in granulomas of patients with sarcoidosis as compared with tuberculous granulomas (31). It still needs to be established if a higher proportion of M2 macrophages identifies a profibrotic mechanism inherent to the pathogenesis of sarcoidosis rather than as a part of a generalized wound-healing mechanism to lung inflammation and injury (30, 31). Further, activated macrophages secrete cytokines that attract and stimulate proliferation, promote survival and migration of fibroblast mediated by platelet-derived growth factor (PDGF) (32). In a recent study, inhibition of M2 macrophage polarization has been shown to inhibit bleomycin-induced IPF in rats (33). Similarly, Wang et al. reported that treatment with microcystin-leucine arginine ameliorates PF through suppressed $CD206^+$ M2-like macrophage polarization by blocking EMT and fibroblast-myofibroblast transition (FMT), and also substantial reduction of TGFβ1/Smad signaling in rat pulmonary tissues (34). Thus, pro-fibrotic processes such as EMT, FMT, and TGFβ1/Smad signaling represent potential targets in mitigating the development and/or progression of PF (**Figure 1**). Supporting the profibrotic role of M2, a recent study showed attenuation of M2 macrophage infiltration in the lung to significantly protect mice against bleomycin-induced lung injury and fibrosis through suppression of Sart1 by small interfering RNA-loaded liposomes (35).

The macrophage-based pathways implicated in PF majorly include signaling pathways such as TGFβ/Smad (36–39), Wnt/beta-catenin (37, 40–42) and interleukin signaling (43–45). Other signaling pathways reported in a limited number of studies include Lrp5/beta-Catenin (46), MAPK (23), Notch (47), PI3K-AKT-mTOR (48, 49), STAT1 and NF-kappaB (50), IGF-1 receptor (51), 4-1BB (52), NRG-1/ErbB4 (53) and M-CSF/M-CSFR (54). Deciphering the molecular mechanisms of macrophage involved in the development of PF, M2 macrophage was shown to promote EMT through the TGFβ1/Smad2 pathway in bleomycin-induced PF mouse model (39). The PF has been alleviated by pirfenidone through suppressed Wnt/GSK-3beta/beta-catenin and TGFβ1/Smad2/3 signaling pathways (37), and by neohesperidin through TGFβ1/Smad3 inhibition (36); whereas, multiwall carbon nanotubes has been reported to mediate macrophage activation and PF progression through induced TGF-beta/Smad signaling pathway (38).

Macrophage M2 promotes myofibroblast differentiation and is associated with pulmonary fibrogenesis. This process is mitigated by suppressed Wnt/beta-catenin signaling through pirfenidone (37), salinomycin administration (40), and targeted inhibition by PRI-724 (41) and ICG-001 (42). The IL signaling is implicated in PF by IL-4–mediated M2 polarization with elevated Gab 1/2 docking proteins (43), by IL-4Ralpha pathway through crystalline silica exposure (45), or by IL-13 pathway in macrophages induced through sphingosine-1-phosphate receptor-2 (44). Also, activation of p38 MAPK signaling pathway mediated through loss of a transcription factor Forkhead box M1 (FOXM1) in macrophages was shown to promote PF. Regarding its molecular substance, activation of p38 MAPK pathway in macrophages was reported with the production of pro-fibrotic mediators IL1β, IL6, and TNFα that stimulated fibroblast activation and survival, thus, exacerbating PF (23). Thus, the interplay between M1/M2 macrophage phenotypes has been suggested to play a key role in the development and progression of lung fibrosis (**Figure 1**).

MICRORNA-BASED REGULATION OF MACROPHAGE POLARIZATION IN IMMUNE RESPONSE, INFLAMMATION, AND FIBROSIS

miRNAs and Their Regulatory Role Towards Macrophage Phenotypes

MicroRNAs (miRNAs) are transcriptional regulators that participate in lung inflammatory responses (5, 55) and are also shown to mediate macrophage polarization. The macrophage subtypes release a various spectrum of cytokines and chemokines that are either pro-inflammatory (M1 phenotypes) and sometimes pro-inflammatory with enhanced tissue destruction, or wound healing and tissue repair (M2 phenotypes), both of which are also regulated through miRNAs (**Table 1**). As an example, miRNA-regulated macrophage polarization is strongly related to miRNA-124, miRNA-155, and miRNA-223. Briefly, higher expression of miRNA-124 attenuates M1 macrophage, whereas miRNA-155 promotes M1 and miRNA-223 depletion also produces M1 polarization (56) (**Supplementary Table S1**). The **Supplementary Table S1** lists a wide spectrum of miRNAs involved in macrophage polarization along with their target proteins and their plausible roles in regulating lung fibrosis.

The regulatory roles of microRNA-mediated macrophage activation and polarization in immune response and inflammation have been extensively reviewed (57–59).

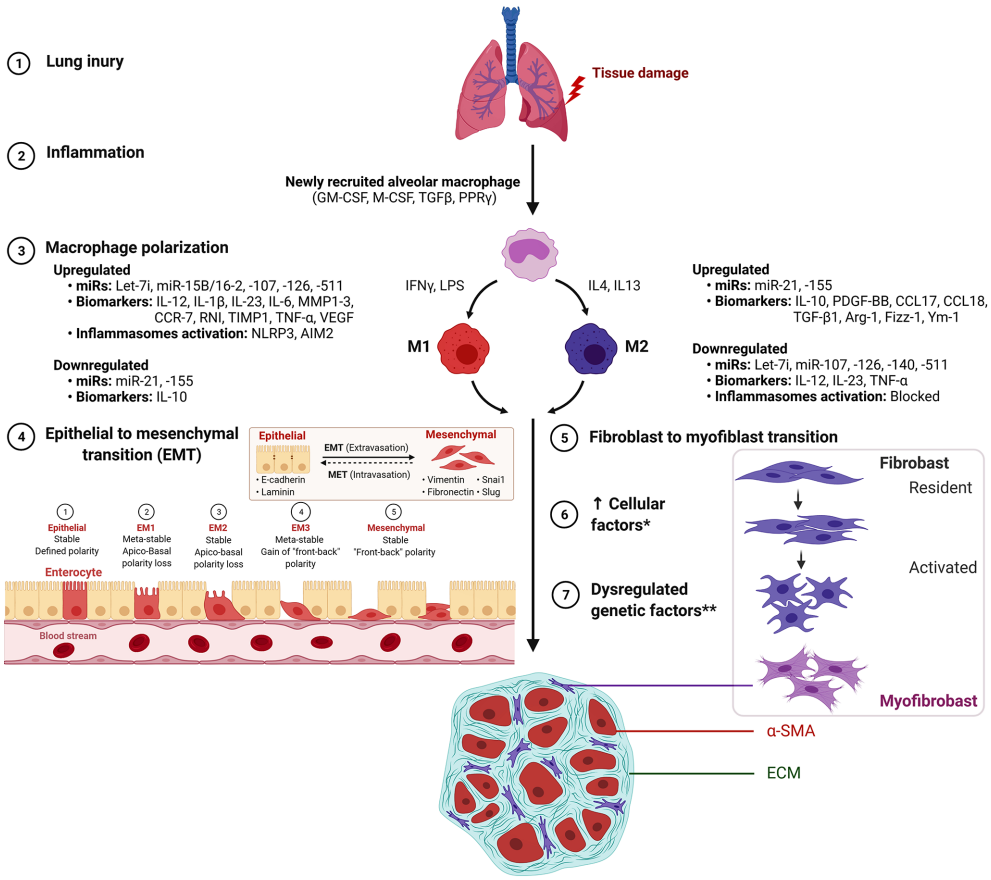

FIGURE 1 | M1 macrophage and M2 macrophage polarization during the development of pulmonary fibrosis. *Increased cellular factors include proliferation, α-smooth muscle actin (α-SMA), matrix factors, collagen, growth factors and cytokines. **Dysregulated genetic factors include upregulated miR-21 and miR-155 and down-regulated Let-7i, miR-107, mir-126, miR-140 and miR-511. Figure created with BioRender. *AIM2*, absent in melanoma 2; *ARG1*, Arginase 1; *Fizz1/RETNLB*, resistin like beta; *Ym1/Chil3*, chitinase-like 3.

This and the following section, therefore, updates the findings of miRNA-mediated macrophage polarization and modulation of pro-inflammatory M1 and/or pro-fibrotic M2 phenotypes in lung disease, in particular, lung fibrosis.

MicroRNA-17, miR-20a, and miR-106a (miR-17/20a/106a) have been shown to effectively regulate alveolar macrophage inflammatory responses such as macrophage infiltration, phagocytosis, and proinflammatory cytokine secretion through targeting leukocyte signal-regulatory protein-α (SIRPα) in both *in-vitro* and *in-vivo* assays (60). The up-regulation of miR-33 in alveolar macrophages exhibited the M1 phenotype with elevated pro-inflammatory cytokines and was demonstrated to promote granuloma formation in a murine model of chronic granulomatous disease, resembling human sarcoidosis pathology, through the suppression of anti-inflammatory lipid transporters (61). An over-expression of macrophage miR-34a has been demonstrated to favour pro-inflammatory M1 phenotype and inhibition of M2 polarization in lipopolysaccharides (LPS) induced acute lung injury (ALI) in mice (62). Similarly, miR-155 was shown to be induced during the macrophage inflammatory response and it orchestrated inflammatory cytokine production in tumour-associated macrophages (TAM). The pro-inflammatory effect of miR-155 has been indicated to promote fibrosis mediated by cross-signaling between macrophages and fibroblasts that governed upregulation of collagen synthesis through TGFβ1 signaling (63). Jaiswal et al., (64) reported overexpression of Let-7c and miR-99a miRNAs in murine bone marrow-derived macrophages (BMDMs) to mitigate Angiotensin-II-induced M1 phenotype activation and to promote M2 phenotype. This inhibition of miR-99a was further shown to reduce ovalbumin-induced Th2 dominance and alleviate allergic airways inflammation (64).

There have also been reports of miR-124 acting to attenuate M1 macrophages as a universal regulator of macrophage into the M2 subtype by decreasing NFκB activity in various subsets of monocytic cells and tissue-resident macrophages including lung macrophages (65, 66). The dysregulation of miR-142-5p and miR-130a-3p was characterised as an important factor governing the polarization of macrophages with higher levels of M2-like phenotypic markers and was associated with airway remodelling

in ovalbumin-sensitized mice (67). Another miRNA, miR-146a has been reported to modulate macrophage polarization by inhibiting Notch pathways in RAQ264.7 macrophage cell lines (68). In this context, we observed an elevated level of miR-146a in pulmonary sarcoidosis inflammation (69). Concerning miRNAs involvement in TAM polarization miR-146a-5p, miR-324-5p, miR-223-3p, miR-223-5p, miR-21, miR-125a, miR-130a, and miR-155a were characterized as oncogenic miRNA, while, miR-1207 and miR-320a as a tumour suppressor miRNA in lung cancer including non-small-cell lung carcinoma (NSCLC) (70). These reports thus emphasize the important role of miRNAs in regulating M1/M2 macrophage polarization in lung diseases in general.

Potential Role of Macrophage-Derived microRNAs in Pulmonary Fibrosis

The microRNA crosstalk influences epithelial-to-mesenchymal and fibroblast-to-myofibroblast transitions implicated in process of macrophage polarization. However, to date, only limited studies have explored the miRNA-based genetic regulation of macrophage polarization and its role in lung fibrosis. An overexpression of let-7c was reported in alveolar macrophages from fibrotic lungs in a bleomycin-induced mouse model as compared with normal lungs, and thus, indicated upregulation of let-7c in macrophages to mitigate M1 phenotype while promoting M2 phenotype polarization (71). Duru et al., (72) reviewed the miRNA-based regulation of macrophage polarization with M2 predominant population in radiation-induced lung fibrosis (RILF) and characterized miR-21 and miR-155 as pro-fibrotic, while let-7i, miR-107, mir-126, miR-140, and miR-511 as anti-fibrotic (72). The IL4 and IL13 induced increased expression of miR-142-5p and downregulated miR-130a-3p transcripts were reported to regulate macrophage profibrogenic expression in tissue samples of patients with IPF (73). The macrophage miR-155 was reported to promote lipopolysaccharide-induced ALI in mice and rats (74). Similarly, miR-155$^{-/-}$ in murine lung macrophages and fibroblasts, and in human IPF lung fibroblasts was implicated in exacerbated pathogenic PF (75). In another study, miR-140 was reported with a key protective role against RILF by inhibiting myofibroblast differentiation and inflammation, and its loss was suggested to induce lung fibrosis through reprogramming fibroblasts and M2 macrophages (76). The role of non-coding RNAs in modulating macrophage phenotypic plasticity and functional heterogeneity among different fibrotic diseases has been recently reviewed (77). These reports further highlight the plausible role of macrophage-derived microRNAs in PF.

Macrophage-Derived Exosomal miRNAs Mediate Pulmonary Fibrosis

Exosomes are cell-derived vesicles produced by several cell types that function in signaling between cells. Exosomes carry a variety of different biomolecules, such as cytokines and microRNAs, and their content may vary from progenitor or target cells. Exosomal miRNAs have also been implicated in interstitial lung diseases including pulmonary sarcoidosis (55) and IPF (78). Recently, interest has also been gained to decipher the role of macrophage-derived exosomal microRNA (miRNA) in lung fibrosis. Exosomal miRNA-328 from M2 macrophages was shown to enhance pulmonary interstitial fibroblast proliferation and promote the progression of PF in a rat model (78). Besides, macrophage-derived exosomes have been recently suggested to mitigate PF progression *via* delivery of antifibrotic miR-142-3p to alveolar epithelial cells and lung fibroblasts by repressing transforming growth factor β receptor 1 (TGFβ-R1) (79). Another study demonstrated that miRNAs contained in alveolar epithelial type-I cells derived-EVs are actively delivered into alveolar macrophages, subsequently promoting inflammasome activation, neutrophil recruitment, and M1-macrophage polarization and thus endorse pro-inflammatory responses in bacterial lung infection (80). In ALI, young mesenchymal stem cells-derived extracellular vesicles (MSC-EVs) showed higher expression of miR-223-5p and lower levels of miR-127-3p and miR-125b-5p compared with aging MSC-EVs. Further, inhibition of miR-127-3p and miR-125b-5p in BMDMs was reported to downregulate M1 and thus, supported their role in M1 macrophage polarization (81). Besides, MSC-EVs were reported to mitigate ALI at least partially through the transfer of miR-27a-3p to alveolar macrophages and promoted M2 macrophage polarization (34). MiR-27a-3p was also shown to target NFKB1 and thus, was suggested as a key regulator of M2 macrophage polarization (34). Recently, a study investigated the potential connections between arsenic and epigenetic changes that mediate M2 macrophage polarization in the development of PF and reported arsenite, elevated LncRNA H19, c-Myc, and Arg1 along with decreased let-7a to be associated with PF in mice (82). Another recent study in a mouse model reported MSC –derived exosomal miR–135b to promote M2 polarization of synovial macrophage by targeting MAPK6, thus mitigating cartilage injury (83). Thus, evidence supports the role of M2 macrophage-derived exosomal miRNA in pulmonary interstitial fibroblast proliferation and in promoting the progression of lung fibrosis. This is further supported by MSC–EVs-derived miRNAs that are suggested to mediate M2 macrophage polarization in the development of PF (34). In ALI, young and aging MSC-EVs harbours differentially expressed miRNAs associated with M1/M2 macrophage polarization (81).

CONCLUSION

The present minireview summarizes major findings on the role of macrophage polarization in diseases, in particular, PF. The non-coding regulatory miRNAs are also discussed in the context of their modulation of M1/M2 macrophage phenotypes in the development and progression of IPF. Further, exosomal miRNA from M2 macrophages favouring pulmonary interstitial fibroblast proliferation and promoting the progression of PF are also described.

In summary, the regulation of macrophage polarization by miRNA is suggested to represent one of the key pathogenetic factors in the development and progression of PF. Further research focused on distinct levels of these processes will

undoubtedly provide updated information. Apart from detailing our current theoretical knowledge, it could be translated into future diagnostic approaches and/or designing novel therapeutic strategies helping to combat IPF, which despite the advancements still constitutes a major debilitating disease.

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AK and MP contributed to the conception and writing of this review. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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