EDITORIALS

MicroRNA Control Lipid-laden Alveolar Macrophages in Smokers: A Potential Therapeutic Target for Chronic Obstructive Pulmonary Disease?

Chronic obstructive pulmonary disease (COPD) is a major health problem and, worldwide, is the third leading cause of mortality according to the WHO (World Health Organization). It is mainly caused by exposure to inhaled noxious particles, such as cigarette smoke (CS) and air pollution, although genetic and epigenetics factors are also involved. Cigarette smoking is the major environmental risk factor and is a contributing factor in more than 80% of patients with COPD. This disease is a chronic lung inflammatory disorder characterized by progressive and irreversible airflow limitation (1).

COPD physiopathology is multifaceted, with oxidative stress, inflammation, and protein/antiproteinase imbalance contributing to tissue destruction associated with lung remodeling. Inflammation involves resident cells, including alveolar macrophages (AMs) (the first-line defense of the respiratory system), together with the recruitment of leukocytes, macrophages, and neutrophils (2). Notably, the increase in AM number is correlated with COPD severity. AMs are critical immune-effector cells whose functions include pathogen clearance and responses to inhaled environmental exposures (3, 4). Chronic exposure to CS alters their phagocytic function, microbicidal activity, and responses to pathogen-associated molecular patterns (3, 5). CS exposure rapidly leads to lipid accumulation in AMs arising from decreased cholesterol efflux, resulting in lipid-laden (foamy) macrophages (6–8). Although AMs normally ingest and degrade oxidized surfactants, during COPD, the generation of oxidized surfactants is markedly amplified by CS exposure, and dysfunction of lipid efflux leads to lipid accumulation in AMs (8). This process is responsible for cell activation and promotes lung inflammation by upregulating cytokine production.

Among factors modulating macrophage function, evidence accumulated over the past decade has demonstrated the important role of microRNAs (miRNAs) in tuning macrophage differentiation, polarization, and activation (9, 10). Moreover, miRNAs have been shown to be involved in COPD pathogenesis. Many miRNAs, including miR-223, miR-1274a, miR-101, miR-132, miR-195, and miR-144, inhibit/activate a range of cellular and molecular signaling pathways (Smad, TGF-β [transforming growth factor-β], Kras, Notch, and others), which are involved in COPD physiopathology (11–17). These molecules, known as epigenetic regulators, work by targeting a variety of cellular and molecular signaling pathways controlling gene expression by targeting specific miRNAs for degradation or translational repression (14). It has been shown that a variety of exogenous (such as CS and oxidative stress) and endogenous (such as dysregulation of various growth factor ligands) factors can induce or modulate miRNA expression. These events are associated with changes at both molecular and cellular degrees and may contribute to the progression of COPD.

In this issue of the *Journal*, Zhu and colleagues (pp. 695–707) report on studies of miRNA in COPD pathogenesis and specifically in the control of AM, one of the first cells exposed to CS (18). They focused their study on miR-103a, a miRNA strongly expressed in myeloid cells and involved in non–small-cell lung cancer (NSCLC) and bronchiolitis obliterans syndrome (19, 20). Zhu and colleagues also report that the miR103a expression is strongly decreased in AMs from both smokers and patients with COPD, an effect directly linked to the consequences of CS exposure as showed by *in vitro* experiments (18). However, the defect in miR-103a is similar between smokers and patients with COPD, and it remains to be determined if this is a marker of CS exposure or if it contributes to COPD physiopathology. Interestingly, a recent study revealed that the expression level of miR-103, in association with other miRNAs, might represent a link between both COPD and NSCLC, as miR-103 expression is inversely correlated with tumor stage and size (20). Indeed, miR-103 can inhibit cell proliferation and limit tumor progression in NSCLC.

In addition, Zhu and colleagues demonstrated that the modulation of miR-103a by CS is related to both cytoplasmic and mitochondrial oxidative stress, a result supported by the inhibitory effect of an antioxidant (N-acetylcysteine) (18). In addition, exposure of macrophages to an oxidative stress (H_2O_2) also inhibits miR-103a expression, whereas modulation of mitochondrial stress did not affect the miR-103a expression. It might also be interesting to evaluate its expression in leukocytes such as neutrophils and dendritic cells, both being potential cell targets. The link between oxidative stress and modulation of miR-103a remains to be defined, although some interactions with the nuclear factor–erythroid 2-related factor 2 pathway have been suggested (21). Further analyses are required to decipher this mechanism.

Functionally, miR-103a directly controls lipid metabolism in macrophages and specifically low-density lipoprotein receptor (LDLR) mRNA and membrane expression (18). Indeed, *in vitro* and *in vivo* experiments confirmed that miR-103a controls lipid accumulation in macrophages and the expression of LDLR. However, Sonett and colleagues reported that lipid storage in CS-exposed macrophages is related to impaired cholesterol efflux associated with decreased *ABCA1* expression (22), a modulation not found in the present study. This suggests that lipid accumulation in AMs could affect complementary mechanisms targeting both lipid endocytosis and efflux.

The subsequent burden of lipids in macrophages triggers an inflammatory response characterized by the release of cytokines, including IL-1α and metalloproteases (22). Both proinflammatory cytokines and proteases play a key role in the physiopathology of COPD by amplifying inflammatory cell recruitment and airway

remodeling. Interestingly, miR-103a also has the ability to modulate mRNA expression of metalloproteases such as *ADAM10* (19, 23) and interleukins (*IL-1β* and *TNFα*) (18). However, the role of miR-103a during the response to CS in murine experimental models needs further study, as does the relationship between the inflammatory status, the disease severity, and the expression of this miRNA in patients with COPD. In a murine model of asthma, miR-103 has been shown to target TLR4 (a pattern recognition receptor also implicated in COPD) and by this mechanism to participate in the control of the inflammatory reaction (24). On the basis of these data, we can hypothesize that modulation of miR-103a might be a way to control the deleterious consequences of chronic exposure to CS to determine its possible therapeutic potential. Recently it has become clear that miRNAs (as well as larger RNAs) can be transferred between cells in mammals by extracellular vesicles, thereby modulating biological processes in recipients (25). However, it remains to be seen whether the delivery of miRNA mimics can affect the expression of target genes and can elicit unwanted pathways. Therefore, numerous hurdles must be overcome in determining the potential of miR-103, alone and in association with other miRNAs, as a therapeutic option for COPD. ■

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