Editorial

# Circular RNAs—a missing piece in pulmonary macrophage activation in silica-induced inflammation

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Silicosis is a progressive, fibrotic pulmonary disease caused by inhalation and deposition of silica particles ($SiO_2$) into lung cells. It occurs most commonly as an industrial disease of people working in the quarrying, manufacturing and building construction. Unfortunately, the disease develops slowly and latently, therefore manifestation of first symptoms occurs even couple years after exposure. Moreover, despite the either changes in place of residence or employment, the patient' disease subsequently progresses. According to recent studies, silicosis is a significant risk factor and seems to be highly related to development of various pulmonary diseases, including chronic obstructive pulmonary disease, lung cancer and tuberculosis. Possibility to develop mentioned pulmonary diseases is about 4-fold higher in silicosis patients compared to general population. In some populations over 50% cases of tuberculosis were related to previous lung silicosis (1-5).

Until today, there are lack of appropriate and highly effective diagnostic tools for early disease detection. The most commonly observed symptoms of lung silicosis include cough, shortness of breath and fever. These uncharacteristic symptoms are accompanied by progression of pulmonary inflammation. The trigger mechanism for disease promotion is deposition of $SiO_2$ particles in the alveoli of the lungs. As result, the increased phagocytosis demonstrated by lung macrophages initiates inflammatory response. Large amounts of collagen is produced by stimulated fibroblasts as a response to stimulation by macrophages. Summarizing, exposure to silicon dioxide affects lung fibroblast proliferation and migration, that participate the inflammatory cascade causing lung fibrosis (1,6-9). The disease initiation and progression are a complex sequence of pulmonary events which include acute and chronic inflammation and fibrosis under different cellular and molecular requirements. Most recently, Yang *et al.* demonstrated completely novel approach to silica-induced pulmonary macrophage activation and explored new pathway of silica-induced inflammatory response with the participation of circular RNAs (circRNAs) (10). The circRNAs are a new class of non-coding RNAs that possess significant capabilities in gene regulations, therefore those are carefully investigated as a potential missing piece in the development of various human diseases. The crucial function of circRNAs is their activity as microRNA sponges, hence circRNAs expression can be related to inhibition of microRNA regulatory pathways (11-13). Yang *et al.* explored role of circZC3H4 RNA in silica-induced macrophage activation using animal mice model and set of macrophage cell cultures. The upstream molecular mechanism and functional effect of circZC3H4 RNA on cell proliferation and apoptosis was investigated. The ZC3H4 was a newly identified protein that belongs to the family of CCCH-zinc finger proteins and regulates immune response by the effects on cytokine productions and immune cell activation (14,15). Authors assumed crucial role of ZC3H4 in the activation of alveolar macrophages and in the development of silicosis. They revealed a novel regulatory mechanism of circZC3H4 RNA/ZC3H4 in silicosis that contributes to the progression of pulmonary fibrosis. Based on a conducted assay the following conclusions were drawn: the silica

dioxide particles significantly increased circZC3H4 RNA expression resulting in higher ZC3H4 protein expression; moreover, silica particles indirectly promoted fibroblast proliferation and migration via circZC3H4 pathway. Finally, authors proven that studied circRNA and ZC3H4 protein participated in silica-induced activation of macrophage. One more important goal was achieved. The mediation of macrophage activation is probably due to direct targeting of miRNA-212 by circZC3H4 RNA, therefore authors speculated that in studied pathway the ZC3H4 protein is regulated via miRNA-212. Further bioinformatics analysis revealed the presence of complementary base pairs in studied circRNA and miRNA-212 (10,16,17). There is only one study that also investigated circRNA role in silicosis mediation. Cao *et al.* explored $SiO_2$ induced endoplasmic reticulum stress in association with enhanced expression of sigma-1 receptor (σ-1R). Authors noted increased migration and proliferation of fibroblasts previously exposed to silica particles as a result of endoplasmic reticulum stress and inhibition of σ-1R. According to researchers circHIPK2 is involved in regulation of σ-1R pathway due to its ability to act as a sponge for miRNA-124 and 506 and throughout promotes fibroblast activation. Specific knockdown of circHIPK2 with siRNA confirmed its role in fibroblast activation induced by silica particles, suggesting that circHIPK2 can be considered as a potential biomarker for early silicosis detection and potential therapeutic target (18).

Summarizing, the study results demonstrated competing endogenous effects of circZC3H4 and miRNA-212 that contribute to activation of alveolar macrophages throughout upregulation of the ZC3H4 protein. The connection between silica-induced macrophage activation and the circRNA/ZC3H4 pathway provided a new insight into potential use of ZC3H4 for management and development of new treatment strategies for silicosis. Perhaps, understanding role of circRNAs in silicosis development allowing early detection of the disease. Also, circRNAs should be further investigated as novel promising therapeutic targets for silicosis to prevent overactivation of pulmonary inflammatory response and fibrosis, because current perspectives of silicosis treatment are poor. There are also limitations of quoted study. Above findings, however promising require exploration in a clinical setting with enrollment of selected group of patients, because the studied model was examined only in a cell culture. The question is whether circRNA/ZC3H4 mechanism and then triggered proliferation of fibroblast, and migration by macrophages truly occur in actual pulmonary fibrosis. Role of circRNAs is still disputable in initiation of human diseases, thus studied mechanisms with the involvement of circRNAs should be carefully considered.

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