

Silica-related diseases in the modern world: A role for self-DNA sensing in lung inflammatory diseases

Occupational silica dust exposure induces inflammatory and fibrotic lung disease such as silicosis, often considered as a disease of the past. However, a recent contribution in this journal highlights new causes of silicosis and reviews the clinical patterns of silicosis, which still represents a major concern of pneumoconiosis for man, lacking effective therapeutic treatment beside lung transplantation.¹

While protective measures could drastically prevent occupational silica exposure, they are insufficiently implemented. Understanding the pathogenesis mechanisms involved in silicosis should help identify novel therapeutic targets. How silica particles cause inflammation and progressive fibrosis is still unresolved, and

merits further investigation. The activation of several pathways has been established.¹ These include the activation of TNF α , alarmins, and NLRP3 inflammasome/IL-1 β axis following crystalline silica engulfment by alveolar macrophages, but also reactive oxygen species production and lysosomal damage, as important drivers of inflammation, as reviewed.¹

We wish to add a new dimension to this landscape, involving the recently characterized nucleic acid-sensing pathways which show that stimulator of interferon genes (STING) is essential for silica-induced lung inflammation. Indeed, exposure to silica particles induces cell stress and cell death in vitro and in vivo, leading to the release

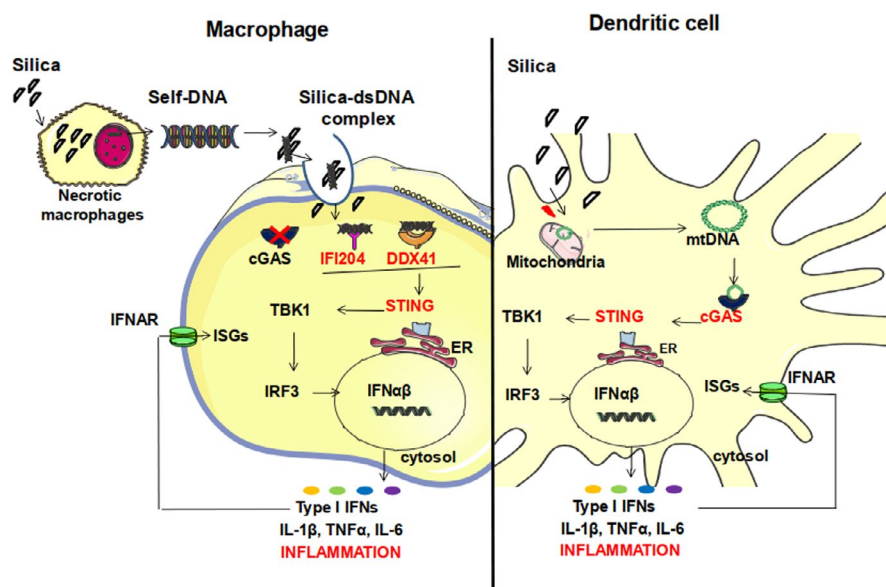


FIGURE 1 Silica-induced inflammation through DNA sensors/STING/type I Interferon (IFN) pathway in macrophage and dendritic cell. Silica microcrystals induce cell stress characterized by mitochondrial damage and release of mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) into the cytosol, and cell death with release of mtDNA and nDNA in the extracellular milieu. Ectopic self-DNA is internalized by macrophages and is sensed by cytosolic sensors that trigger the stimulator of interferon genes (STING) pathway. In vitro silica-exposed macrophages are activated by extracellular DNA, leading to STING-dependent type I IFN response, and this seems independent of cyclic GMP-AMP synthase (cGAS), but involving DEAD-box helicase 41 (DDX41) and IFN- γ -inducible protein 204 (IFI204) DNA sensors. In dendritic cells, silica exposure-induced mtDNA engages cGAS to form 2'3'cGAMP and activates STING. After self-DNA recognition, STING recruits the TANK-binding kinase 1 (TBK1), which dimerizes and autophosphorylates; activated TBK1, in turn, phosphorylates STING, creating a docking site for the IFN regulatory factor 3 (IRF3); IRF3 is phosphorylated by TBK1, leading to IRF3 dimerization and translocation to the nucleus where it triggers IFN α and IFN β gene expression, inducing downstream type I IFN responses with activation of interferon-simulated genes (ISG). STING activation also leads to NF- κ B activation and the production of pro-inflammatory cytokines

of self-DNA of nuclear and mitochondrial origin in the cytosol and extracellular space.² This release of self-DNA, in turn, activates the DNA sensor/STING pathway and drives type I interferon (IFN) expression and related inflammation.² In vitro, mitochondrial double-stranded DNA (dsDNA) is sensed by cyclic GMP-AMP synthase (cGAS) and STING in dendritic cells, while in macrophages extracellular dsDNA activates STING via other DNA sensors independently of cGAS after silica exposure (Figure 1). In vivo, cell-free dsDNA is detected in the bronchoalveolar fluid and serum upon experimental lung exposure to silica, leading to IFN-I-driven inflammation.² This response to silica exposure is prevented in mice deficient for cGAS, STING or type I IFN receptor. Importantly, self-DNA degradation by administration of DNase I attenuates silica-induced lung inflammation in mice.²

Silica exposure is a known factor diminishing host resistance to lung infections, especially increasing the risk of pulmonary mycobacterial infection, but the underlying mechanism is unclear. We propose a role for silica-induced DNA sensing activation in reducing host resistance. Indeed, host control of mycobacterial infection relies on type 1 immunity. However, we found that silica pre-exposure activates the DNA/cGAS/STING pathway and increases the type 1 IFN response to mycobacterial infection that, in turn, enhances type 2 immunity and favours infection in mice.³

In summary, silica exposure-induced cell stress/death causes mitochondrial and nuclear self-DNA release which is recognized by the DNA sensors cGAS and STING and triggers lung inflammation. Such pathogenesis based on self-DNA recognition pathways may be involved more broadly in lung inflammation.⁴ Indeed, self-DNA release activating the cGAS/STING pathway is involved in several models of inflammatory lung diseases in mice such as exposure to cigarette smoke,⁵ allergens⁶ and ozone (unpublished), which depend on cGAS and/or STING expression. This may contribute to the additive joint effects of combined silica exposure and cigarette smoking on mortality.¹ Both cGAS and STING are druggable, and several small molecules which target these respective pathways are currently in pharmaceutical development.

In conclusion, the recent discoveries suggest that targeting self-DNA or DNA sensors such as cGAS/STING needs to be explored and may lead to novel therapies of silicosis and other severe inflammatory lung diseases.

KEYWORDS

basic mechanisms, dendritic cells, inflammation, innate immunity, interferons, lung diseases other than asthma and COPD, macrophages

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