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Review Article

Silica binding and toxicity in alveolar macrophages

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Abstract

Inhalation of the crystalline form of silica is associated with a variety of pathologies, from acute lung inflammation to silicosis, in addition to autoimmune disorders and cancer. Basic science investigators looking at the mechanisms involved with the earliest initiators of disease are focused on how the alveolar macrophage interacts with the inhaled silica particle and the consequences of silica-induced toxicity on the cellular level. Based on experimental results, several rationales have been developed for exactly how crystalline silica particles are toxic to the macrophage cell that is functionally responsible for clearance of the foreign particle. For example, silica is capable of producing reactive oxygen species (ROS) either directly (on the particle surface) or indirectly (produced by the cell as a response to silica), triggering cell-signaling pathways initiating cytokine release and apoptosis. With murine macrophages, reactive nitrogen species are produced in the initial respiratory burst in addition to ROS. An alternative explanation for silica toxicity includes lysosomal permeability, by which silica disrupts the normal internalization process leading to cytokine release and cell death. Still other research has focused on the cell surface receptors (collectively known as scavenger receptors) involved in silica binding and internalization. The silica-induced cytokine release and apoptosis are described as the function of receptor-mediated signaling rather than free radical damage. Current research ideas on silica toxicity and binding in the alveolar macrophage are reviewed and discussed.

Keywords: Scavenger receptor; Macrophage; Silica; Free radicals; MARCO; SR-A; Immune modulation

Contents

Abbreviations: RR, relative risk; AM, alveolar macrophages; PL, phospholipids; SP, surfactant proteins; PMN, polymorphonuclear leukocyte (neutrophils); DPPC, dipalmitoyl phosphatidyl choline; ROS, reactive oxygen species; RNS, reactive nitrogen species; $O_2^{\bullet -}$, superoxide anion; $HO^{\bullet}$, hydroxyl radical; $NO^{\bullet}$, nitric oxide; MnSOD, manganese superoxide dismutase; GSH, glutathione; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; MEK, MAP/ERK kinase; AP-1, activating protein 1; NF-κB, nuclear factor κB; LPS, lipopolysaccharide; JNK, Jun N-terminal kinase; TNF-α, tumor necrosis factor α; IL-1β, interleukin 1β; MIP, macrophage inflammatory protein; MCP, monocyte chemotactic protein; IL-8, interleukin 8; SR, scavenger receptors; ox-LDL, oxidized low-density lipoprotein; ac-LDL, acetylated low-density lipoprotein; SR-A, scavenger receptor A class; SRCL, scavenger receptor with C-type lectin; SCARA5, class A scavenger receptor type 5; SRCR, scavenger receptor cysteine-rich C-terminal region; MSR, macrophage scavenger receptor; MARCO, macrophage receptor with collagenous structure; CHO, Chinese hamster ovary; HSP, heat-shock protein; PKC, protein kinase C; Th, T helper; IL-12, interleukin 12; IFN-γ, interferon-γ; TLR, toll-like receptor; ICAM-1, intercellular adhesion molecule 1; IL-13, interleukin 13; APC, antigen-presenting cell; IL-4, interleukin 4; DC, dendritic cell; NZM, New Zealand mixed mice.

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Introduction

Silicon (Si) is the second most abundant element on earth next to carbon. A Si atom combined with two oxygen (O) atoms creates silicon oxide or silica (SiO_2), naturally occurring as quartz or sand. There are multiple crystalline forms and one amorphous form of silica. Inhalation of the crystalline form of silica has been historically associated with the development of a severe respiratory disease, silicosis, which is a lung pneumoconiosis characterized by alveolar proteinosis and diffuse fibrosis resulting in progressively restrictive lung function [1]. Silicosis has been primarily associated with long occupational exposures to crystalline silica that typically occur in sandblasting, silica milling, rock drilling, and tunneling [2,3]. There is evidence that silica exposure can also be linked to the development of autoimmune diseases such as scleroderma (systemic sclerosis), rheumatoid arthritis, chronic renal disease, and lupus [4]. Additionally, silica inhalation is believed to be the cause of some rare lung cancers [5], although significant relative risk (RR) of lung cancer is associated only with individuals who already have silicosis from silica exposure [6]. Based on the relative dose–response or exposure–response relationships in experimental animal studies, silica seems to be a uniquely hazardous particle type [7].

Given the diversity of pathologies associated with silica exposure, it is unlikely that one common mechanism is responsible for all of the possible diseases. Although the exact sequence of events (from silica inhalation to disease) is not known, it is generally accepted that the alveolar macrophage (AM) is a relevant cell type to study [1]. Because the role of the AM is to clear the lung of inhaled debris, it is reasonable to assume that the macrophage is the first cell of the body that will have significant contact with the inhaled silica particle. Upon contact, the AM will bind to the silica and begin to engulf the particle. If the AM survives the silica encounter, it will likely migrate out of the lungs to either the proximal lymph nodes or through the mucosal–ciliary escalator and eventually out of the respiratory tract [8]. If the AM stays in the lung it will migrate to the interstitial space and become an activated interstitial macrophage (IM) that could contribute directly to pathogenesis [9]. Some research indicates that the IM may play an important role in the progression of silica-induced lung disease [10,11].

Investigators studying the AM/silica particle interaction have developed several hypotheses to describe how silica is toxic to AM. Some explanations of toxicity focus on the surface qualities of the silica such as free radicals and surface charge. Others suggest that silica can cause the AM to self-destruct by apoptosis or lysosomal disruption, which could lead to the development of autoantigens. The purpose of this review article is to present all of the current research regarding silica toxicity of the AM, because most researchers in this area would agree that the initial toxicity of the AM is an important first step in the development of disease.

Surface modifications of inhaled silica by lung surfactant

Before the inhaled silica particles are encountered by AM, lung surfactant composed of phospholipids (PL) and surfactant proteins (SP) could potentially coat the outer surface of the silica particles, modifying the surface chemistry and ultimately influencing the toxicity. This interaction can be further complicated by free radical modifications of the phospholipids and proteins occurring on surface contact with the silica. Some research has focused on this aspect of silica toxicity by using surfactant components in in vitro and in vivo toxicity models. An illustration of this process can be found in Fig. 1.

Effect of silica exposure on lung surfactant

It has been known for some time that silica inhalation is associated with increased PL and SP in the lung. Early studies in animal models indicated a general increase in surfactant volume, but not composition in response to silica [12,13], which, according to Muller et al., is unique to silica inhalation compared to tobacco smoke and diesel particles [14]. One study found three- to sevenfold increases in PL and SP, respectively, occurring in a rat model with acid-washed silica, but not with unwashed silica [15]. Another study found sustained elevations (in weeks) in PL and SP-A in response to silica [16]. Several other studies found silica-induced increases in PL and SP [17,18], including specific increases in SP-A [19,20], SP-D [19,21], vitamin E [22], and phosphatidyl inositol [23]. In contrast, Seiler et al. found a dose-dependent decrease in phosphatidyl glycerol in response to silica [23].

The sources of increased surfactant production after silica exposure are the alveolar type II cell and the bronchiolar epithelial cell [1]. There is some evidence that the AM, in response to silica stimulation, signals the type II cell to produce more surfactant [24]. Isolated type II cells after silica-induced lung injury were found to have increased SP-A receptor activity [25], indicating that the increase in surfactant production may be receptor regulated. The exact trigger of surfactant overproduction is not well described, but it is believed that there is cell-to-cell communication between AM, type II cells, and epithelial cells resulting in increased PL and SP. Kanj et al. suggest that