ABSTRACT | Background: The relationship between silica dust and tobacco smoking as enhancers of pulmonary fibrosis development has not yet been well established. Some pathophysiological mechanisms which might support this relationship were postulated. The role of different cells involved in the inflammatory response, and of different biological pathways needs to be recognized. These facts encouraged us to perform the present descriptive review. Results: Growing evidence suggests that local inflammation induced by exposure to silica dust and tobacco smoking might be modulated by genetic factors, epigenetic mechanisms, autoimmune reactions and local hypoxia, giving rise to the epithelial–mesenchymal transition. These phenomena lead to accumulation of necrotic material in the lungs, which contributes to inflammation’s perpetuation and to an exaggerated innate immunological response among workers with silicosis who smoke. Conclusion: Direct comparisons of different measurement studies of inflammatory biomarkers associated with silicosis and tobacco smoking should be performed cautiously due to several possible confounding factors, such as compartmentalization or interaction among the various biological pathways and cell types involved. Ventilation systems should be improved and exposure reduced to prevent lung damage in workers exposed to silica. In regard to smoking cessation, psychotherapy approaches are needed for early prevention of lung damage.

Keywords | silica; silicosis; smoking; biomarkers.

RESUMO | Introdução: A relação entre a sílica e o tabaco como potencializadores na geração de fibrose pulmonar não foi ainda bem estabelecida, embora tenham sido postulados alguns mecanismos fisiopatológicos para embasá-la. É necessário reconhecer o papel das diversas células envolvidas na resposta inflamatória, assim como as diversas vias biológicas que participam na gênese. Esses fatores nos motivaram a desenvolver a presente revisão descritiva. Resultados: Cada vez mais evidências sugerem que a inflamação local produzida por exposição à sílica e à fumaça do tabaco pode ser modulada por fatores genéticos, mecanismos epigenéticos, reações autoimunes e hipóxia local, levando à transição epitélio-mesênquima e ao acúmulo de material necrótico no pulmão, o que contribui para a perpetuação da inflamação e a uma resposta imunológica inata exacerbada nos trabalhadores com silicose fumantes. Conclusão: Comparações diretas de diferentes estudos de mensuração de biomarcadores inflamatórios associados à silicose e ao tabagismo devem ser realizadas com cautela, devido a uma série de possíveis fatores de confusão, como compartimentalização ou interação com as diversas vias biológicas e tipos celulares envolvidos. Convém destacar que para se evitar a ocorrência de dano pulmonar nos trabalhadores expostos à sílica, devem-se melhorar os sistemas de ventilação e reduzir sua exposição. No contexto da cessação do tabagismo, é necessário o uso de componentes psicoterapêuticos, com o fim de evitar o dano pulmonar precocemente.

Palavras-chave | sílica; silicose; tabagismo; biomarcadores.
INTRODUCTION

The relationship between silica dust and tobacco smoking as enhancers of pulmonary fibrosis development has not yet been well established. Tobacco smoking is currently considered a risk factor for lung disease, because it tends to generate a profibrotic response, just as silica dust does. Active or ex-smokers are 60% more likely to develop interstitial fibrosis.

Some pathophysiological mechanisms which might support the relationship between smoking and silica were postulated. As it's known, silica dust induces oxidative stress, increases epithelial apoptosis, interferes with the regulation of immune response and induces recruitment of inflammatory cells, especially macrophages. Also, tobacco smoking induces epigenetic changes that persist after cessation.

Current smokers exhibit higher hypermethylation, DNA-methyltransferase-1 levels and reduced histone deacetylase-2 function. These changes have been associated with the fibrogenic process which occurs along the progression of the lung damage induced by silica.

Silicosis is currently described as an interstitial/inflammatory disease of the respiratory system which causes permanent damage to the lung parenchyma and the bronchial tree as a consequence of an inflammatory influx triggered by inhalation of silica particles. This is a complex multifactorial disorder that results from the interaction between inhaled inorganic particles and a dynamic and irreversible chronic inflammatory response. These inflammatory processes might ultimately modify lung mechanics, resulting in pulmonary fibrosis and airflow changes.

The Inflammation affects all areas in the respiratory system, including lung parenchyma and central and small airways. However, although inflammation is a key feature of the reaction to inorganic silica particles, its contribution to pathophysiology and progression of silicosis are not fully understood.

Similarly, neither the exact mechanisms involved nor the role of different inflammatory components are clear. Within this context, a more detailed characterization of the entire repertoire of inflammatory responses in silicosis may pave the way for a deeper understanding of the disease's pathogenesis.

Unfortunately, the number of inflammatory mediators and their complex interrelations have prevented the development of a simple pathogenetic model. As a result, numerous questions still do not have an answer in biomedical research.

In this way, it is necessary to recognize the role of the different cells involved in the inflammatory response associated with silica and tobacco, as well as the different biological pathways involved in its genesis. These facts encouraged the development of the present descriptive review.

RESULTS

The initial inflammatory response induced by silica particles in the pulmonary alveoli, chronically maintained by continue exposure, is considered the main risk factor for the development of silicosis. Pathological changes might be induced in the long run, which finally lead to the known abnormalities that characterize this occupational lung disease, which is asymptomatic at first and ends in massive pulmonary fibrosis (Figure 1).

This description is based on the current evidence, which indicates that different aspects of the inflammatory response are abnormal in silicosis, ultimately increasing the recurrent inflammatory burden, not only due to exposure to silica particles, but also to the reaction in each individual as a function of their singular characteristics. Therefore, it is necessary to highlight some of the main features of silica-related inflammation.

Local inflammation in workers with silicosis is a complex process characterized by inflammatory cells infiltration in the pulmonary alveoli, followed by increased expression of cytokines, chemokines, enzymes, growth factors and adhesion molecules.

Further, the process involves a considerable number of different cell types, including macrophages, neutrophils, eosinophils, histiocytes, epithelial cells, endothelial cells, dendritic cells, lymphocytes, fibroblasts and pneumocytes.

In addition, local inflammation in acute silicosis is closely associated with various biological pathways, including abnormal cell signaling, increased oxidative stress, protease-antiprotease imbalance and induction of apoptosis, among others (Figure 2).

Growing evidence suggests that local inflammation might be modulated by genetic factors and epigenetic mechanisms, the respiratory tract microbiota, age, autoimmune
reactions and local hypoxia, giving rise to the epithelium–mesenchymal transition. The latter is the process by which the epithelial cells acquire the mesenchymal phenotype.

All these factors participate in complex interactions, which influence in different ways the extension of lung damage, evidenced by elevation of the serum NSE and CA125, which accounts for the clinical expression of silicosis in some cases. In workers with silicosis, local inflammation is driven by an abnormal or exaggerated response to inhaled tobacco smoke.

Although a similar pattern of inflammation might develop among smokers without silicosis, in those with it inflammation seems to be characterized by more a pronounced structural lung damage.

The molecular mechanisms underlying the exaggerated inflammatory response in silicosis have not yet been fully elucidated, but they involve both innate and acquired immunity. Exposure to silica and tobacco smoke is associated with deterioration of the macrophages’ ability to eliminate respiratory pathogens and apoptotic cells (Figure 3).

In silicosis, the number of macrophages in the respiratory tract increases. Development of persistent colonization suggests that the elimination of bacteria by phagocytosis is defective. This ultimately results in abnormal bacterial

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**Figure 1.** One of the features of silicosis is continuous stimulation of macrophages in fibroblast development, even after exposure to silica ceased.
colonization and a vicious circle between inflammation and infection.

Furthermore, migration of aberrant neutrophils occurs in silicosis, which promotes tissue damage as a result of excessive proteinase release. Changes in the acquired immunity were also reported, corresponding to an abnormal response to tobacco smoking involving regulatory T cells, increase of type 1 T helper cells (Th1) and participation of Th17 cells20.

Altogether, current evidence suggests that silicosis is characterized by deregulation of many aspects of inflammatory response, whose net effect is the increase of inflammatory burden due to NALP3 inflammasome activation. Investigation on the possible persistence of local inflammation, even after smoking cessation, is another relevant issue in silicosis (Figure 4).

The effects of smoking cessation on local inflammation among workers with silicosis are still controversial. However, there is evidence that smoking cessation at an early stage effectively reduces the inflammatory reaction induced by silica particles, which points to the potential benefits of smoking cessation in the early stages of the disease. Epithelial cells and macrophages are probably the first cell types to meet tobacco smoke and, therefore, the first to act and trigger the inflammatory response.

The involvement of the alveolar epithelium in the pathogenesis of silicosis associated with tobacco smoking has three main aspects. First, as physical barrier, the epithelial cells of the respiratory tract are important for lung defense, with production of mucus by goblet cells, dendritic cells22, and secretion of antioxidants, anti-proteases and defensins, in addition to the constant ciliary movement. Tobacco smoke and other harmful agents might possibly modify the response of the respiratory tract epithelium, thus contributing to the lesion produced and increasing the susceptibility to infections. Second, through contact with inflammatory mediators, epithelial cells are activated by tobacco smoke and start producing inflammatory mediators, including TNF-α, IL-1β, IL-623,24 and granulocyte-macrophage colony stimulating factor (GM-CSF) — activated by chemokines25 and macrophages. All these factors play a crucial role in

![Diagram](image-url)

**Figure 2.** Apoptosis plays a highly relevant function in living beings, because it enables the destruction of damaged cells. This process is accelerated in silicosis, with consequent increase of the progression of inflammation.
inflammation and in the damage to the lung tissue. In addition, the epithelial cells of the small airways might be an important source of transforming growth factor beta, which causes local fibrosis. Finally, pneumocytes are also susceptible, and changes might occur at this level. In this sense, the presence of vascular endothelial growth factor (VEGF) seems to be necessary to maintain the integrity of the alveolar cells. By the same token, the lack of action of this factor gives rise to emphysema as secondary disorder.

Macrophages are the main phagocytes of the respiratory system. They maintain the sterility of the lower respiratory tract, which is often colonized with microorganisms, mainly bacteria. In patients with silicosis, sharp increase (5 to 10 times) on the number of macrophages has been described in the airways, lung parenchyma, bronco-alveolar lavage fluid and sputum (Figure 5).

There is clinical evidence indicating that the activation of alveolar macrophages by silica causes rapid and sustained inflammation, characterized by secretion of monocyte chemotactic protein 1 (MCP-1) which induces fibrosis. This finding provides a new perspective on MCP-1’s potential to contribute to the development of new therapeutic strategies for silicosis.

The elevation of the number of macrophages in the lungs of smokers and workers with silicosis is caused by increased recruitment of circulating monocytes in response to CKLF1 monocyte-selective chemokines. However, despite this increase in the number of macrophages in the respiratory

Figure 3. Innate and acquired immunity afford effective defense against the many pathogens around us. However, infections are common among individuals with silicosis and smokers.
**Figure 4.** Inflammasome is responsible for the activation of inflammation, and induces cell pyroptosis—a programmed cell death mechanism different from apoptosis.

**Figure 5.** Macrophages are presented to T helper cells, and thus warn T-cells about the presence of a foreign body. For not being digestible, silica particles stimulate the multiplication of these cells.
tract of smokers with silicosis, persistent colonization is a common finding. These phenomena suggest that these cells have reduced the ability to phagocyte bacteria found in lung, particularly *Haemophilus influenzae* and *Streptococcus pneumoniae*, in comparison to healthy individuals. In addition, not only bacterial elimination is impaired, but macrophages also fail to remove apoptotic cells. The result is accumulation of necrotic material in the lungs, which contributes to perpetuate inflammation and to an exaggerated innate immune response among smoking workers with silicosis.

Increase of adaptive immune system cells, both T-lymphocytes and CD8 was also described. This increase is relevant for two reasons: first, because it seems to be one of the main differential aspects of the inflammatory infiltrate among workers with silicosis who do not smoke. Second, because there is a correlation between the number of T-cells, extension of alveolar destruction and severity of airflow obstruction among workers with silicosis who smoke.

**CONCLUSION**

The understanding of the biological mechanisms underlying silica-induced lung damage has increased significantly in recent years. However, it is still far from the point that would allow focusing on the identification of new inflammatory biomarkers. This goal demands a more thorough comprehension on the basic mechanisms of inflammation in silicosis.

Direct comparisons of different measurements in studies of inflammatory biomarkers associated with silicosis and tobacco smoking should be performed cautiously, as a function of several possible confounding factors, such as compartmentalization or interaction among the various biological pathways and cell types involved.

The studies conducted up to the present time specifically focused on a small number of inflammation biomarker candidates. Future studies should be designed with a broader approach encompassing the main inflammatory aspects of silicosis, including the identification of markers of early exposure to silica particles and markers able to detect lung involvement. Identification of biomarkers able to track both local and systemic inflammation induced by the presence of silica in the lung tissue might be achieved through rigorous and well-designed studies.

Identification of potential factors known to be sources of inflammation, and their correlation with higher risk of silicosis will provide mechanistic clues to this question. As knowledge evolves, we will be able to understand better the development and perpetuation of this disease, which will allow us to identify new therapeutic targets.

Efforts to identify the genetic determinants of silicosis have evolved together with the available technologies, which include two different and complementary approaches. In one case, the analysis of candidate genes is based on the hypothesis that there is one specific gene related with disease, and thus seeks to evaluate whether this relationship does indeed exist. Then, high-performance technologies, such as microarray analysis, allows testing up to one million single nucleotide polymorphisms (SNP) simultaneously. This approach is not based on any hypothesis, and therefore opens new venues of research. Similarly, identification of protective genotypes for silicosis opens a window to the eradication of this global occupational respiratory disease across the world. It should encourage us to continue exploring the relationship between polymorphisms of the IL-4-33 gene site and silicosis, as protective genotype for workers exposed to inorganic silica particles.

Finally, it is worth observing that, in order to prevent lung damage among workers exposed to silica, ventilation systems, dust removal, isolation, wet techniques and personal protection, including appropriate respirators which reduce exposure, should be improved.

Regarding smoking cessation, the application of psychotherapy resources with demonstrated efficacy is necessary, including development of skills, problem solving training, coping techniques and social support.

The aim of this article is to sensitize occupational physicians and workers’ health authorities to the magnitude of the problem represented by this lung disease, which does not only impair the physical health of workers, but also has an impact on their family, community, and even on the country as a whole.

**ACKNOWLEDGMENTS**

The authors want to thank Dr. Sofia Jimenez and Dr. Miguel Rodriguez for their contributions that much improved the English version of the manuscript. We are specially indebted to Eustorgio Delgado Palma for his revision of the Spanish version, resulting in a scientific article targeting divulgation among a high-level academic readership.
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