Original Article

OVERVIEW OF THE LARGEST HEALTH HAZARD: PNEUMONO ULTRAMICROSCOPE –DETECTED SILICOVOLCANOCONIOSIS

Thirumalaikumaran Rathinam[1], Prema S[2], Mahalakshmi D[3], Mohamed Musharaf B[4], Praveen Kumar B[5]

[1]Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, Saveetha Nagar, Thandalam, Chennai – 602 105.
[2]Crescent School of Pharmacy, BS Abdur Rahman Crescent Institute of Science and Technology, Vandalur, Chennai 600048.
[3]Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, Saveetha Nagar, Thandalam, Chennai – 602 105.
[4]Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, Saveetha Nagar, Thandalam, Chennai – 602 105.
[5]Saveetha College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, Saveetha Nagar, Thandalam, Chennai – 602 105.
Corresponding Author: Dr. Thirumalaikuamaran Rathinam
E-mail: kumarancognosist@gmail.com

DOI: 10.47750/pnr.2023.14.S02.147

Abstract

A lung illness with the longest English word (45 letters) **pneumono ultramicroscopic silicovolcanoconiosis** Inhaling sand and silica dust can lead to the lung irritation that results in silicosis. The earth's crust has the most silica minerals. Affected individuals are those who breathe in the fine silica dust while working in the mining or construction industries. Silicosis is a degenerative condition that has no known treatment. Infections like mycobacterial infection, fungal infection, and TB are caused by it. This article outlines the several types of silicosis, as well as it historical context, epidemiology, diagnosis and therapy. The progression of silicosis is thought to be intimately related to programmed cell death (PCD), which includes autophagy, apoptosis and pyro ptosis, according to our hypothesis in this review and additionally, proteins plays a significant role in formation and development of silicosis. In conclusion, more in depth study on these mechanism and impact may be anticipated to become interesting candidates for silica therapy or intervention in future**[1].**

KEYWORDS: Acute and chronic silicosis, Programmed Cell Death (PCD), autophagy, apoptosis, pyro ptosis.

INTRODUCTION:

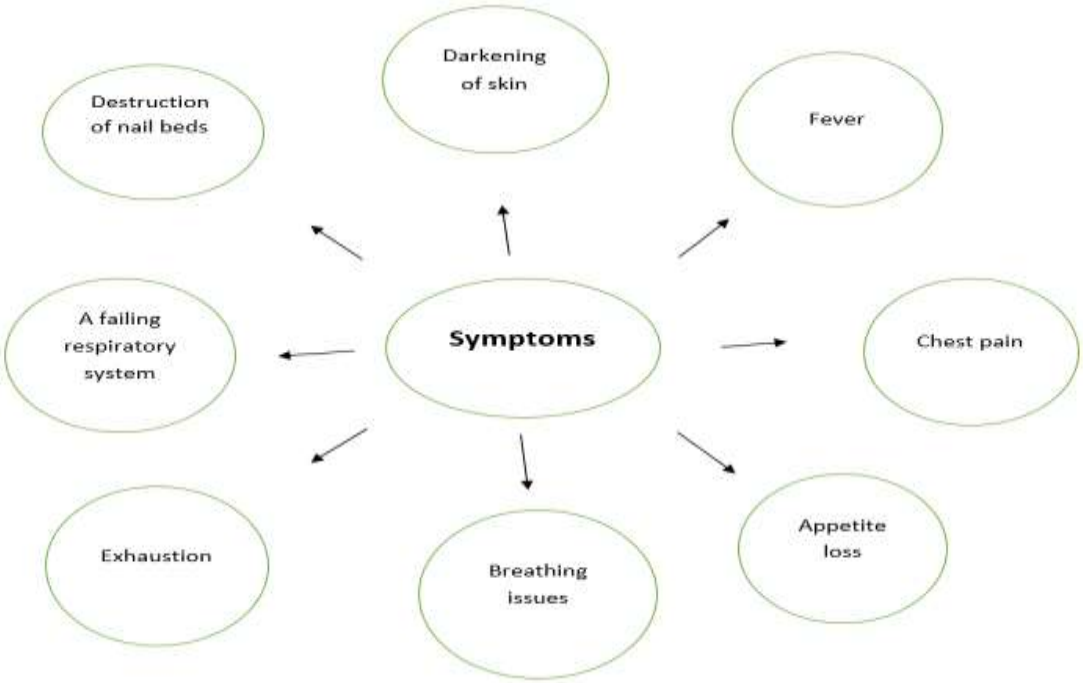
The inhalation of significant amounts of silica dust during an prolonged amount of time may result in the development of silicosis, a potentially fatal, irreversible, fibrotic lung illness. Silicosis typically only manifests itself after significant exposure at work. The illness has a protracted latent period and can manifestly used in medicine as an accelerated, chronic, or acute disease. It is a form of pneumoconiosis.

Cough, shortness of breath, cyanosis, and fever are some of the signs of acute silicosis. the name silicosis, which dates back to 1870 and is derived from the Latin word silex, or flint. Ancient Greeks and Romans were aware of the respiratory issues brought on by breathing in dust.

Agricola recognized lung issues in miners brought on by dust in a book he wrote in the middle of the 16th century. As people migrated away from hand tools and toward machines as a result of the fast industrialization **[2-3].**

SIGNS AND SYMPTOMS:

-Signs and symptoms of chronic silicosis take years to manifest following exposure**[4].**



PATHOPHYSIOLOGY:

When silica dust is inhaled, it becomes embedded in the ducts and small alveolar sacs in the lungs.

There is an exchange of O_2 and CO_2. Ingesting dust particles and producing leukotriene B4, interleukin-1, and other cytokines can trigger an inflammatory reaction.

Encourage the production of collagen by surrounding the silica particle And Fibroblast proliferation. Nodular lesions are created by the fibrosis. Crysttaline silica's inflammatory action can be mediated by the NALP3 inflammasome.

In acute silicosis, microscopic pathology reveals Cellular infiltration of the alveolar walls and Alveolar exudate that contain periodic acid schiff positively**[5].**

HISTORICAL ASPECT:

Throughout history, crystalline silica-related respiratory illness has been documented. In 1690, Lohneiss reported that when "the dust and stones fall against the lungs, the men develop lung sickness, breathe with difficulty." Hippocrates mentioned the condition of "breathlessness" in miners. According to the Metropolitan Life Insurance Company, employees at quarries and machine shops as well as foundries missed work a lot more frequently than other workers in the 20th century. This presents the first contemporary argument for exposure to silica has clinical significance. However, silicosis was not formally recognised as a significant public health issue until the so-called Hawk's Nest Tunnel accident in the early 1930s **[6-7].**

EPIDEMIOLOGY:

Occupational silicosis: The most prevalent occupational lung disease in the world is silicosis, which is prevalent globally but is more prevalent in developing nations. Between 1991 and 1995, China reported more than 24,000 deaths attributed to silicosis annually. Between one and two million American workers are thought to have been exposed to crystalline silica dust at work, and 59,000 of those workers would eventually develop silicosis. CDC data show that silicosis is not common in the United States. Between 1968 and 1999, the death rate decreased by 84%, with only 187 deaths occurring in that year. New Jersey Silicosis Cases Are Strongly Linked to Industry and Occupation. Prior to the fast industrialization brought about by the use of pneumatic drilling and mine explosions, silicosis was presen**t**. The "Hawks Nest Tunnel Disaster" was regarded as the worst industrial accident in American history **[8-10].**

Non-Occupational silicosis: Desert Lung Conditions (Dust Pneumonia) enduring contact with sand dust in arid regions leads to silicosis in its non occupational form; cases have been documented from the Sahara. The buildup of this sand particles in the environment is what causes the sickness. Additionally, it is supposed to be an infectious illness. Al Eskan was brought on by organic antigens found in silica following the Gulf War in 1930. But it's unknown why silica particles are connected to silica **[11-14].**

Acute silicosis: When contrasted to chronic silicosis, it can entail distinct types of damage processes. By using electron microscopy, acute silicosis may be seen to primarily impact the lungs and show hypertrophy lining the alveoli are type ll pneumocytes . The production of proteinaceous material and surfactant protein by these hypertrophic pneumocytes may contribute to the emergence of silicotic lung disease**[15]**. When compared to intact silica, fractured silica may have larger levels of free radicals, which could lead to a harsher inflammatory response. high levels of free radicals may affect how transcription factors are activated, causing harm to cells and/or DNA. Acute silicosis has historically been linked to jobs like rock drilling and sand blasting that produce recently cracked silica particles that can be associated with those occupational specifically **[15-20].**

Chronic silicosis: It is linked to long-lasting inflammatory alterations in the alveoli. Pulmonary fibrosis could arise as a result of this chronic alveolitis disease. Although the exact cause of this silicosis is yet unknown, it is thought to be brought on when lung cleansing silica particles are phagocytosed by alveolar macrophages. Alveolar macrophages may suffer damage if they are unable to remove silica particles from the lungs in a timely manner **[21]**.this kind of damage causes macrophages to get activated, create extra free radicals, reactive oxygen species (ROS), and reactive nitrogen species (RNS). Release of transcription factors (NFkB and activator protein 1) leads to the creation and release of proteases, metabolites of aryl hydrocarbons (leukotriene-B4, prostaglandin E), and inflammatory cytokines (TNF AND IL-1 & 6). By attracting type II pneumocytes and fibroblasts, which have the capacity to produce significant amounts of fibronectin and collagen, the continual generation of fibrotic factors may contribute to silicotic lesions. A TNF antibody treatment in mice has been shown to reduce MIP-2 production, inflammation, and the ensuing pulmonary fibrosis **[22]**. TNF single nucleotide polymorphisms and gene-gene interaction have been reported to be more common in former miners with severe silicosis-related lung illness. Alveolar macrophages may be stimulated when silica particles are ingested, but they may not be killed, according to a theory. The synthesis of collagenase and subsequent lung parenchymal lung damage may occur from this macrophage activity**[25-27].**

PROGRAMMED CELL DEATH IS NECESSARY FOR SILICOSIS:

Development of Silicosis and its impact of Autophagy, apoptosis and pyroptosis;

1. *Autophagy's impact*:

A kind II planned cell death is what autophagy is known as. It can "digest the trash of cells" and is widely present in eukaryotic cells **[28-29].**

1.1 The intricate function of autophagy in numerous signalling pathway when silicosis develops:

The protein kinase B (PKB/Akt), the mammalian target of rapamycin (mTOR), and phosphatidylinositol 3 kinase (PI3K) signalling pathway has been shown to be the mechanism through which silica controls the activity of autophagy. The silica-induced AM apoptosis is reduced when mTOR inhibitor (Rapa) is used **[30]**.In AMs treated with silica, autophagy decreases the manifestation of tumour necrosis factor (TNF) and TGF**[31]**.Atractylenolide-3, an active component of natural plants, can speed up the autophagic degradation process by supporting the mTOR-dependent signalling pathway**[32]**. The putative natural mTOR activator may be ATL-3. As a result, attacking mTOR may be thought as an effective plan for treating silicosis in clinical settings.

1.2 Evidence suggests that some proteins are involved in the control of autophagy triggered by silica:

There is evidence that several members of protein with Zn- finger CCCH family may have a regulatory role in the silica-induced autophagy. After exposure to silica, protein 1 elicited by monocyte chemo attractant protein 1 (MCPIP1) triggered the activity of macrophage autophagy and stimulated the development of silicosis via the p53 signalling pathway**[33]**.Silica-induced macrophage autophagy and apoptosis were prevented by MCPIP1. The analogous to MCPIP1 like Zn- finger CCCH -type protein with four residues(ZC3H4) enhanced the autophagy and affected endothelial cells' EMT (epithelial mesenchymal transition). The Fluid from the mouse model of silicosis's bronchoalveolar lavage contains an enhanced production of Gas6 (growth arrest specific protein) and its usual receptor has been noted. Gas6 improved the destruction of autophagic degradation **[33-41]**.

2. The toxic effects of silica are linked to apoptosis and pyroptosis:

Early phases of apoptosis help with lung tissue remodelling because it serves as a compensatory mechanism to remove injured cells and inflammation. It has recently been determined that pyroptosis is a process of Host cell death that is triggered by infection of mircrobes, DAMPs, ischemia necrosis products and other factors. In particular, GSDMD is primarily caused by cell inflammatory necrosis during pyroptosis (gasdermin D)

2.1 Regulation of apoptosis in cells induced silica by p53 and Members of Its Family:

Cell apoptosis caused by silica may include p53. Particularly, silica increased p53 transactivation through p53 accumulation in embryo cells and ser 392 p53 phosphorylation. The connection between p53, the serine protease(urokinase-type plasminogen activator -uPA) and anti- fibrinolytic drugs(plasminogen activator inhibitor – PAI) in pulmonary fibrosis has received a lot of attention. uPA mRNA, PAI-1 mRNA, and p53 trans-activation don't interfere with one another. These findings suggest that a potential intervention technique to prevent silicosis may involve inhibiting p53 expression alone or the interaction between p53 and the fibrinolytic system **[42-44].**

2.2 A catalyst for cell pyroptosis that acts as a "irritant" Silica:

Rats with silicosis had higher levels of IL -1 , IL -18, caspase -1 as well as NLR family pyrin domain containing (NLRP3) were found in the lung tissue of these mice. These results support the theory that caspase -1 may be

particularly induced by silica to cleave pro- IL-1 into mature IL-1 , causing cell death via the pyroptosis pathway. An anti- fibrotic effect on silicosis may result from the implantation of Bone marrow mesenchymal stem cells(BMSCs). Another study found that using BMSCs in a rat model of silicosis reduced levels of LC3 and BECN1. It suggests that the restriction of autophagy activity has mitigated pulmonary tissue damage**[45-47].**

DIAGNOSIS:

An extensive history of exposure to silica, usually at work, supports the diagnosis .The development of silicosis is not believed to be significantly influenced by incidental exposures. In conjunction with a history that is compatible with silica exposure of medical significance, **Chest Radiograph** exhibiting nodular opacities are esential. It's crucial to keep in mind that diseases with a similar profile, such as infection of fungi, miliary Tuberculosis, Besnier-Boeck-Schaumann disease, fibrosing alveolitis are included in the differential diagnosis for silicosis. Both chronic and accelerated silicosis exhibit nodular opacities in lung(upper field) on chest radiography . "eggshell" lymph nodes are distinctively calcified thoracic lymph nodes**[48].**

Other assessments to aid in the diagnosis of silicosis include:

• **CT scan**: looks for scar tissue in your lungs.

• **Bronchoscopy**: To examine your lungs for any damage, the doctor will insert a thin tube with a tiny camera into them.

• **Biopsy**: To obtain a sample of a nodule, the doctor will insert a needle into your chest and into your lungs.

• **Sputum test**: This aids in assessing various lung conditions, such as tuberculosis (TB).

PREVENTION:

- Limit the time when you're exposed to silica.
- wear mask when you are working around silica and employer provide proper safety equipment.

Other ways to prevent silicosis:

- Use proper ventilation.
- To cut, chip, or grind things, use wet processes.
- Use different types of blasting media instead of silica-containing ones.
- Wear respirators to prevent exposure to silica.
- Don't drink or eat near silica dust.
- Before you eat, Wash hands and face.
- After work, Shower and change clothes.

TREATMENT:

Silicosis is a disease with no known cure that cannot be reversed. The present focus of treatment is on symptom relief and avoiding complications. These include ceasing use of cough suppressants, cigarettes, smoking, and medications for bacterial lung infections, as well as ceasing exposure to silica and other lung irritants. TB prophylaxis is given to people whose IGRA (interferons-gamma release assays) blood tests for tuberculine skin test results are positive. prolonged anti-tuberculosis treatment for patients with active TB (multi-drug regimen). Chest physiotherapy to promote mucus drainage from the bronchi. It is possible to administer oxygen if hypoxemia is present. bronchodilators to make breathing easier. Lung transplantation is the most successful method of treating damaged lung tissue, although it carries significant hazards of its own. Among the experimental therapies are the inhalation of aluminium powder, polyvinyl nitrate, and D-penicillamine. Tetrandine , a herbal extract, may prevent the spread of silicosis**[49].**

CONCLUSION:

Millions of individuals are at risk from silicosis, which is still the biggest health risk. The debilitating chronic illness is increasingly spreading from the former industrial zones to emerging economies worldwide. The best kind of prevention is primary prevention. Silicosis and illnesses connected to silica can be avoided but not cured. To achieve the target established by WHO and OSHA to eradicate silicosis by 2030, every nation and region should engage on preventive measures.

REFERENCES

1. Definition of pneumonoultramicroscopicsilicovolcanoconiosis in oxford dictionary(british and world English)2012,oxford university press.

2. Muetterties M, O'Halloran Schwarz L, Wang R. Sandblasters. In: Greenberg M,editor. Occupational, Industrial, and Environmental Toxicology, 2nd ed. Philadel-phia, PA: Mosby, 2003.

3. American Conference of Governmental Industrial Hygienists. Threshold limit values and biological exposure indices. American Conference of Governmental Industrial Hygienists (ACGIH): Cincinnati, OH, 2002.

4. Jane A P, Nick V, Vala R K. Pollutants,Human Health and the Environment: A Ris Based Approach. John Wiley & Sons. 2012.p. 273.

5. GBD 2013 Mortality and Causes of Death, Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden Of Disease Study 2013". Lancet. 2014. 385: 117–71.

6. Hunter D. The Disease of Occupations. Little, Brown, Boston, MA: 1962.

7. Jordan J. Hawk's Nest. West Virginia Historical Society Quarterly 1998;12(1):1-3.

8. Safety and Health Topics Silica, Crystalline. Occupational Safety And Health Administration. March 2007.

9. National Institute for Occupational Safety and Health (NIOSH). 2004.

10. Keenan, Steve. Book explores Hawks Nest tunnel history. The Fayette Tribune, Oak Hill,W.Va. Fayettetribune.com. 2008.

11. Nouh MS. Is the desert lung syndrome(nonoccupational dust pneumoconiosis) a variant of pulmonary alveolar microlithiasis?Report of 4 cases with review of theliterature. Respiration. 55 (2): 122–6. 1989.

12. Korenyi-Both AL, Korényi Both AL Molnar AC, Fidelus-Gort R. Al Eskandisease: Desert Stormp neumonitis. MilMed. 1992; 157 (9): 452–62.

13. Griffin DW. Atmospheric movement ofmicroorganisms in clouds of desert dust and implications for human health. Clin Microbiol Rev. 20 (3): 459–77, 2007.

14. OSHA's Final Rule to Protect Workers from Exposure to Respirable Crystalline Silica. www.osha.gov. 2016.

15. Hoffman EO, Lamberty J, Pizzolato P, et al. The ultrastructure of acute silicosis. Arch Pathol 1973;96(2):104-7.

16. Dalal NS, Shi XL, Vallyathan V. ESR spin trapping and cytotoxicity investigations of freshly fractured quartz: mechanism of acute silicosis. Free Radic Res Commun 1990;9(3-6):259-66.

17. Heffner JE, Repine JE. Pulmonary strategies of antioxidant defense. Am Rev Respir Dis 1989;140(2):531-54.

18. Fubini B, Hubbard A. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation by silica in inflammation and fibrosis. Free Radic Biol Med 2003;34(12):1507-16.

19. Ding M, Chen F, Shi X, et al. Disease caused by silica: mechanisms of injury and disease development. Int Immuno pharmacol 2002;2(23):173-82.

20. Surrat P, Winn W, Brody A. Acute silicosis in tombstone sandblasters. Am Rev Respir Dis 1977;115:52

21. Dubois CM, Bissonette E, Rola-Pleszczynski M. Asbestos fibers and silica particles stimulate rat alveolar macrophages to release tumor necrosis factor. Autoregulatory role of leukotriene B4. Am Rev Respir Dis 1989;139(5):1257-64.

22. Fubini B, Hubbard A. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) generation by silica in inflammation and fibrosis. Free Radic Biol Med 2003;34(12):1507-16.

23. Miller BE, Bakewell WE, Katyal SL, et al. Induction of surfactant protein (SP-A)biosynthesis and SP-A mRNA in activated type II cells during acute silicosis in rats.Am J Respir Cell Mol Biol 1990;3(3):217-26.

24. Oghiso Y, Kubota Y. Enhanced interleukin 1 production by alveolar macrophages and increase in Ia-positive lung cells in silica-exposed rats. Microbiol Immunol 1986;30(11):1189-98.

25. Schmidt JA, Oliver CN, Lepe-Zuniga JL, et al. Silica-stimulated monocytes release fibroblast proliferation factors identical to interleukin 1. A potential role for interleukin 1 in the pathogenesis of silicosis. J Clin Invest 1984;73(5):1462-72.

26. Bagchi N. What makes silica toxic? Br J Ind Med 1992;49(3):163-6.

27. Heppleston AG, Styles JA. Activity of a macrophage factor in collagen formation by silica. Nature 1967;214(87):521-2.

28. Hotchkiss, R.S.; Strasser, A.; McDunn, J.E.; Swanson, P.E. Cell death. N. Engl. J. Med. 2009, 361, 1570–1583. [CrossRef]

29. Glick, D.; Barth, S.; Macleod, K.F. Autophagy: Cellular and molecular mechanisms. J. Pathol. 2010, 221, 3–12. [CrossRef]

30. Du, S.; Li, C.; Lu, Y.; Lei, X.; Zhang, Y.; Li, S.; Liu, F.; Chen, Y.; Weng, D.; Chen, J. Dioscin alleviates crystalline silica-induced pulmonary inflammation and fibrosis through promoting alveolar macrophage autophagy. Theranostics 2019, 9, 1878–1892[Cross Ref] [PubMed]

31. Li, N.; Shi, F.; Wang, X.; Yang, P.; Sun, K.; Zhang, L.; Hao, X.; Li, X.; Li, J.Li, Y. Silica dust exposure induces pulmonary fibrosis through autophagy signaling. Environ. Toxicol. 2021, 36, 1269–1277.[Cross Ref]

32. Chen, S.; Tang, K.; Hu, P.; Tan, S.; Yang, S.; Yang, C.; Chen, G.; Luo, Y.; Zou, H. Atractylenolide III alleviates the apoptosis throughinhibition of autophagy by the mTOR-dependent pathway in alveolar macrophages of human silicosis. Mol. Cell. Bio chem. 2021,476, 809–818. [Cross Ref]

33. Liu, H.; Fang, S.; Wang, W.; Cheng, Y.; Zhang, Y.; Liao, H.; Yao, H.; Chao, J. Macrophage-derived MCPIP1 mediates silica-induced pulmonary fibrosis via autophagy. Part. Fibre Toxicol. 2016, 13, 55. [CrossRef] [PubMed]

34.Wang, X.; Zhang, Y.; Zhang, W.; Liu, H.; Zhou, Z.; Dai, X.; Cheng, Y.; Fang, S.; Zhang, Y.; Yao, H.; et al. MCPIP1 regulates alveolar macrophage apoptosis and pulmonary fibroblast activation after in vitro exposure to silica. Toxicol. Sci. 2016, 151, 126–138[CrossRef]

35. Jiang, R.; Han, L.; Gao, Q.; Chao, J. ZC3H4 mediates silica-induced EndoMT via ER stress and autophagy. Environ. Toxicol. Pharmacol. 2021, 84, 103605. [Cross Ref] [PubMed]

36. Jiang, R.; Zhou, Z.; Liao, Y.; Yang, F.; Cheng, Y.; Huang, J.; Wang, J.; Chen, H.; Zhu, T.; Chao, J. The emerging roles of a novel CCCH-type zinc finger protein, ZC3H4, in silica-induced epithelial to mesenchymal transition. Toxicol. Lett. 2019, 307, 26–40.[Cross Ref] [PubMed]

37. Yi, J.H.; Zhang, Z.C.; Zhang, M.B.; He, X.; Lin, H.R.; Huang, H.W.; Dai, H.B.; Huang, Y.W. Role of epithelial-to-mesenchymal transition in the pulmonary fibrosis induced by paraquat in rats. World J. Emerg. Med. 2021, 12, 214–220. [Cross Ref]

38. Jiang, R.; Gao, Q.; Chen, M.; Yu, T. Elk-1 transcriptionally regulates ZC3H4 expression to promote silica-induced epithelial-mesenchymal transition. Lab. Investig. 2020, 100, 959–973. [Cross Ref]

39. Yang, X.; Wang, J.; Zhou, Z.; Jiang, R.; Huang, J.; Chen, L.; Cao, Z.; Chu, H.; Han, B.; Cheng, Y.; et al. Silica-induced initiation of circular ZC3H4 RNA/ZC3H4 pathway promotes the pulmonary macrophage activation. FASEB J. 2018, 32, 3264–3277. [CrossRef] [PubMed]

40. Li, W.; Xie, L.; Ma, J.; Yang, M.; Wang, B.; Xu, Y.; Fan, L.; Mu, G.; Shi, T.; Chen, W. Genetic loss of Gas6/Mer pathway attenuates silica-induced lung inflammation and fibrosis in mice. Toxicol. Lett. 2019, 313, 178–187. [Cross Ref]

41. Li, W.; Xie, L.; Ma, J.; Cheng, M.; Fan, L.; Xu, Y.; Wang, B.; Chen, W. Gas6 or Mer deficiency ameliorates silica-induced autophagosomes accumulation in mice lung. Toxicol. Lett. 2021, 337, 28–37. [Cross Ref]

42. Wang, W.; Liu, H.; Dai, X.; Fang, S.; Wang, X.; Zhang, Y.; Yao, H.; Zhang, X.; Chao, J. p53/PUMA expression in human pulmonary fibroblasts mediates cell activation and migration in silicosis. Sci. Rep. 2015, 5, 16900. [CrossRef]

43. Wang, L.; Bowman, L.; Lu, Y.; Rojanasakul, Y.; Mercer, R.R.; Castranova, V.; Ding, M. Essential role of p53 in silica-inducedapoptosis. Am. J. Physiol. Lung Cell. Mol. Physiol. 2005, 288, L488–L496. [CrossRef] [PubMed]

44. Bhandary, Y.P.; Shetty, S.K.; Marudamuthu, A.S.; Fu, J.; Pinson, B.M.; Levin, J.; Shetty, S. Role of p53-fibrinolytic system cross-talkin the regulation of quartz-induced lung injury. Toxicol. Appl. Pharmacol. 2015, 283, 92–98. [CrossRef]

45. Song, Z.S.; Shao, H.; Chen, Y.Q.; Zhang, R. Expression and significance of NLRP3/IL-1β/TGF-β(1) signal axis in rat model of silicosis pulmonary fibrosis. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 2018, 36, 819–823. [CrossRef] [PubMed]

46. Evavold, C.L.; Ruan, J.; Tan, Y.; Xia, S.; Wu, H.; Kagan, J.C. The pore-forming Protein gasdermin D regulates interleukin-1 secretion from living macrophages. Immunity 2018, 48, 35–44.e6. [CrossRef] [PubMed]

47. Li, X.; Wang, Y.; An, G.; Liang, D.; Zhu, Z.; Lian, X.; Niu, P.; Guo, C.; Tian, L. Bone marrow mesenchymal stem cells attenuate silica-induced pulmonary fibrosis via paracrine mechanisms. Toxicol. Lett. 2017, 270, 96–107. [CrossRef]

48. Ch. 2: Fatal and Nonfatal Injuries, andSelected Illnesses: Respiratory Diseases: Pneumoconioses: Silicosis. Worker Health Chartbook 2004

49. Steenland K, Goldsmith DF. Silica exposure and autoimmune diseases. Am J Ind Med. 1995; 28:5