



ISSN: 2231-3354
Received: 15-06-2011
Revised on: 30-06-2011
Accepted: 04-07-2011

Overview of cytokines and receptors in Silicosis

Shambhoo Sharan Tripathi, Haushila Prasad Pandey and Bholanath Paul

**Shambhoo Sharan Tripathi,
Bholanath Paul**
*Immunobiology Division, Indian
Institute of Toxicology Research,
Lucknow, India.*

Haushila Prasad Pandey
*Department of Biochemistry,
Banaras Hindu University,
Varanasi, India.*

ABSTRACT

Occupational inhalation of crystalline silica for a long period is known to cause silicosis, an irreversible lung damage, often leading to lung fibrosis. It kills thousands of people every year everywhere. The pathophysiology of silicosis involves chronic inflammation of lung due to accumulation of various inflammatory mediators and fibrogenic factors in the airways. In this review we discuss the role of these mediators and their receptors in inducing silicosis and discuss whether inhibitors and decoys can interfere in the induction and onset of the disease.

Key words: Silicosis, Receptors, Cytokines, Fibrosis.

INTRODUCTION

Silicosis is an occupational lung disease caused by long exposure to crystalline silica, killing thousands of people every year throughout world (Wagner, 1996). Though incidence of silicosis have decreased in the developed countries (Bang et al, 2008; Grehardsson, 2002), it is prevalent in developing countries (Lehtiwn & Goldstein, 2002). In India, three million people get exposed to silica dust/flakes especially those working in mines and industries viz. Stone-cutting, silica milling, agate, slate pencil and asbestos industries. A sizeable proportion of workers engaged in construction activities mainly road building, have imminent exposure to silica dust. This lung disease has a long latency period and may be clinically present as an acute, accelerated, or chronic ailment. The pathophysiology of chronic silicosis which involves chronic inflammation in lung is the result of the accumulation of various inflammatory mediators as well as other fibrogenic factors.

Silicosis is the consequence of human exposure to silica. Available silica or the silicon dioxide is actually the compound of element silicon and oxygen formed under increased heat and pressure and is present in nature in crystalline as well as amorphous form. Amorphous silica, except fibreglass, is not generally considered to be harmful to man (Mossman and Churg, 1998). The most abundant form of crystalline silica is quartz, a typical component of rock. All crystalline forms of silica viz. Quartz, cristobalite and some form of tridymite are inherently piezoelectric *i.e.* having the property to produce opposite electric charges on opposite sides of the physical structure when pressure is applied directly to the crystal. It is theorized that this piezoelectric characteristic probably take part in the pathophysiology of silicosis by the generation of reactive oxygen species on the edge of silica molecules and damages alveolar macrophages (Williamson et al, 2001). The silanol (SiOH) group present on the surface of silica particle are capable of forming H-bond with oxygen and nitrogen group found in the biological cell membranes which may subsequently lead to loss of membrane structure, lysosomal leakage, and tissue damage. All these

***For Correspondence:**
Bholanath Paul,
*Immunobiology Division,
Indian Institute of Toxicology
Research, Lucknow 226001, India.*

processes probably contribute in the development of lung scarring (Castranova, 2004).

Different types of clinical and pathological forms of silicosis have been identified which include simple or nodular, silicoproteinosis (acute silicosis), complicated silicosis and interstitial fibrosis. These structural changes against the silica exposure take place as a consequence to interaction to scavenger cells with their receptor and infiltration of inflammatory cells that produces fibrogenetic and inflammatory mediators as well as growth factors, including tumour necrosis factor (TNF- α), interleukin-1 (IL-1), tumour growth factor (TGF- β), macrophage inflammatory protein MIP-1 and MIP-2, interleukin-6 (IL-6) interleukin-4 (IL-4) and interleukin-5 (IL-5) (Vanhee et al, 1995; Driscoll et al, 1993; Driscoll et al, 1990; Jagirdar et al, 1996). Both mediators and growth factors effect cells through their receptor molecule which is either present on cell surface or in soluble form in the cytoplasm. The present review is aimed to discuss the role of cytokines and their cell receptors in silicosis.

MARCO (Macrophage Receptor and Collagenous Structure)

Alveolar macrophages (AMs) play central role in crystalline silica-induced inflammation and pulmonary pathologies (Hamilton et al, 2008; Lehnert et al, 1989). Ostensibly they are instrumental in escalating inflammatory response against inhaled particles (Bowden, 1987). The balance between clearance and retention of crystalline silica in the lungs is maintained by AM playing an imperative role in regulating the inflammatory response and silica induced fibrosis. The whole process of silica clearance is carried out by members of the Scavenger Receptor family named as macrophage receptor with collagenous structure (MARCO), expressed mainly by macrophages, dendritic cells, and certain endothelial cells. Studies have identified MARCO as the key receptor in recognizing crystalline SiO₂ and causing apoptosis in murine AM (Hamilton, 2006). Furthermore, MARCO has also been reported to be a receptor for TiO₂ (Arredouani et al, 2005). However, even though MARCO binds both Crystalline SiO₂ and TiO₂, they show contrasting apoptotic and pathological outcomes (Thakur et al, 2008). Macrophage receptor MARCO is a protein that in humans is encoded by the MARCO gene (Elomaa et al, 1995, 1998; Kangas et al, 1999). This protein gene is a member of the class-A scavenger receptor family and is part of the innate antimicrobial immune system. The protein binds particles and bacteria via intracellular C-terminal, scavenger receptor cysteine-rich (SRCR) domain (Arendouani et al, 2004). In addition to short cytoplasmic and transmembrane domains, there is an extracellular spacer domain and a long, extracellular collagenous domain. The protein may form a trimeric molecule by the association of the collagenous domains of three identical polypeptide chains (Entrez Gene: MARCO macrophage receptor with collagenous structure"). Crystalline silica, but not TiO₂ upregulated MARCO expression on pulmonary macrophages, indicates specific role for MARCO in crystalline silica-induced inflammation. Nevertheless, MARCO plays an important role in removal of crystalline silica particles from the lung (Thakur et al, 2009).

Unsuccessful clearance of crystalline silica may result in persistent inflammation due to prolonged interaction of particles with both immune and non-immune cell populations such as neutrophils, AM, dendritic cells (DCs), and epithelial cells in the lung. Disruption, of the epithelial lining would not only allow cytokines and growth factors released by AM to reach the interstitium and contribute to the development of silicosis (Merchant et al, 1990), but also, enhance translocation of crystalline silica particles to the interstitial space (Warheit et al, 1997). Once located in the interstitium these particles cannot be easily cleared. The interaction between crystalline silica and interstitial macrophage (IM) initiates a cascade of inflammatory signals that are major contributors to progressive fibrotic development in the lung (Adamson et al, 1991).

Interlukine-4 Receptor alpha

In chronic allergic diseases, there is pronounced infiltration of inflammatory cells including lymphocyte, mainly Th2 cells, eosinophils, and mast cells. The Th2 derived IL-4 and IL-13 cytokines engage in recreation a vital task in generation of fibrosis and chemotactic activity of eosinophils (Lukacs et al, 2001; Sempowski et al, 1996; Zhu et al, 1999; Fukuda et al, 1996). These cytokine convey their gesture to other cells like macrophage and fibroblast etc, through common receptor IL-4 receptor alpha (IL-4R α). IL-13 shares many properties with IL-4, due to common receptor subunits (IL-4R α), signal transduction pathways and transcription factors (STAT-6) (Hilton et al, 1996). In the case of silica induced lung fibrosis, these cytokine follow IL-4R α pathway in association with Ym1 secretory protein which is produced by alternatively activated macrophage. The Ym protein was identified in respiratory secretions and was shown to be progressively up-regulated during the development of allergic inflammation in the murine lung. Ym protein is characterized as mammalian lectin and participate in airways wall remodelling in the allergic lung (Webb 2001). Silica treatment to wild type mice increase the Ym1 expression via Ym1-IL-4R α pathways and contributing in Th2 dominated fibrosis (Migliaccio et al, 2008).

Although the vast majority of the literature points to a vital role of Th2 immunity in the generation of pulmonary fibrosis, there are exceptions depending on model and strain.

Interlukin-6 Receptor Alpha

Interlukin-6 (IL-6) exerts as a pleiotropic cytokine (Qiu et al, 2004) important biological effects on inflammation, immunity and stress (Kishimoto et al, 1995; Papanicolaou et al, 1998). Accumulating evidence reveals that IL-6 levels increase in blood (Yokoyama et al, 1995), bronchoalveolar lavage fluid (BALF) (Broide et al, 1992) and lung tissues (Marini et al, 1992) of patients who are suffering from lung disease. Thus, IL-6 may play a significant role in inflammatory processes by inducing cellular adhesion molecules on inflammatory cells which make easy their infiltration in lung (Duits et al, 1991). IL-6 binds to the surface IL-6R [membrane-bound IL-6R (mIL-6R)], leading to the dimerization of gp130/IL-6Rb into tetra- or hexameric structures,

There by forming the active IL-6R complex (Boulanger et al, 2003). Dimerization of gp130 by IL-6 causes the activation of several signalling pathways including the Janus kinase (Jak) and signal transducers and activators of transcription (STAT) pathway. Activation of Jak1, 2 and Tyk2 (Tyrosine kinase 2) by IL-6 results in the phosphorylation and activation of STAT-3 and, to much lesser extent, STAT-1 leading to the induction of IL-6 responsive gene expression (Lutticken et al, 1994; Stahl et al, 1994; Akira et al, 1994; Nakajima et al, 1995). In silica induced lung fibrosis IL-6R play an important role in regulation of Th2 cytokines (IL-4 and IL-5) expression which is proved by gene silencing of IL-6R gene (Tripathi et al, 2010). Thus IL-6 receptor regulates the fibrosis in response to silica by modulating the profibrotic cytokines.

Tumour Necrosis Factor Receptors (TNFR) I & II

In response to silica, inflammation and fibrosis engender is closely attached with the activity of TNF- α and its receptors, TNFRI (p55) and TNFRII (p75). The transgenic attenuation of both TNF- α receptors, TNFRI and TNFRII, confirmed reduced fibrogenic response of endotracheal silica exposure (Ortiz et al, 1999). Exposure of macrophages to silica induces TNF- α mRNA and protein (Claudio et al, 1995; Barrett et al, 1999). The binding of TNF- α to its receptor triggers phosphorylation and destruction of I κ B (the inhibitor of NF- κ B in the cytosol), which allows NF- κ B to enter the nucleus. NF- κ B is activated by silica in alveolar macrophages and other lung cells by mechanisms involving the hydroxyl radical, and in turn regulates the production of TNF- α and other inflammatory mediators. These mechanisms are important in the pathogenesis of silica-induced lung diseases (Chen and Shi, 2002; Hubbard et al, 2002).

In vivo studies utilizing TNFR gene ablation models and anti-TNF antibodies or soluble receptors demonstrated attenuation of silica-induced fibrogranulomatous disease with inhibition of TNF- α activity (Piguet et al, 1990; Piguet and Vesin, 1994). In other study, it has been verified in vivo that silica dependent induction of chemokines, including Monocyte chemoattractant protein-1 (MCP-1), Interferon gamma-induced protein-10 (IP-10), macrophage inflammatory protein (MIP-1 β , MIP-2 and MIP-1 α), is in part mediated by TNF- α signal transduction via the TNFRI receptor (Pryhuber et al, 2003).

Fas ligand (FasL)

During silicosis it is seen that various anomalies develop such as production of autoantibodies and many complication of autoimmune disease (Otsuki et al, 2003). Fas/FasL pathway plays a role in pathogenesis of autoimmune diseases by regulating the apoptosis. It is a membrane bound and shed protein belonging to the TNF gene family, and counter-receptor for the death-promoting Fas molecule expressed by variety of lymphoid and non-lymphoid tissues (Nagata, 1999). Lymphocyte apoptosis mediated by Fas/FasL interaction regulates immune responses (Lenardo et al, 1999) and FasL-mediated apoptosis of leukocyte prevent inflammatory reaction at immune-privileged site (Griffith et al, 1995). Some researcher has reported that in silicosis patients

apoptosis of BAL cells are inversely proportional to lung function (Szczelek et al, 2004). In another experiment it has been shown that FasL expression and silica induced apoptosis decreases in rat model (Corsini et al, 2003).

CONCLUSION

Silicosis is one of the oldest occupational disease known to mankind. It is an incurable pulmonary disease caused by inhalation of dust containing free crystalline silica. It is irreversible and the disease progress even when exposure to causal factor stops. After exposure, silica particle are encountered with macrophage where it is being cleared with the help of MARCO receptors present on macrophages. In response to silica macrophages release different kinds of proinflammatory cytokines which act on other inflammatory cells *viz.* Th cells, fibroblast, eosinophils etc. via their receptors by means of autocrine as well as paracrine mode of action.

Occupational exposure of silica leads to the production of large group of inflammatory and fibrotic mediators that are implicated in the development of fibrotic lesion. Various factors including free radicals, ROS, RNS, Lipid peroxide, TNF, IL-1, IL-6, IL-8, IFN, specially take part in inflammatory reaction, whereas TNF, TGF and IL-4, seems to be implicated in fibrotic processes. Among the cytokine TNF play important role in inflammation by controlling other cytokines like IL-1, IL-4, IL-6 and IL-8 while IL-6 regulate the fibrosis by modulating the expression of Th2 cytokines.

In fact all these receptors are a door for entrance of signal in the inflammatory cells so as to make intracellular communication among themselves and construct the network of inflammatory response. As suppressor of cytokine signalling especially Socs3 that can negatively regulate Stat3-Janus kinase pathway- the anti-inflammatory pathway, it may be a candidate molecule to address for therapeutic benefit against lung fibrosis. Use of siRNA to knockdown persistent expression of Socs3 may help prevent development of lung fibrosis following particulate exposure. Alternatively, use of receptor decoys may help prevent the onset of silica induced lung fibrosis.

REFERENCES

- Adamson IY, Letourneau HL, Bowden DH: Comparison of alveolar and interstitial macrophages in fibroblast stimulation after silica and long or short asbestos. *Lab Invest* 1991;64: 339-344.
- Akira S, Nishio Y, Inoue M, et al: Molecular cloning of APRF, a novel IFN-stimulated gene factor 3 p91-related transcription factor involved in the gp130-mediated signaling pathway. *Cell* 1994;77: 63-71.
- Arendouani M S, Yang Z, Ning Y, Qin G, Soininen R, Trygvasan K and Kobzik L: The scavenger receptor MARCO is required for lung defense against pneumococcal pneumonia and inhaled particles. *J Exp Med.* 2004; 200: 267-272.
- Arredouani MS, Palecanda A, Koziel H, et al: MARCO is the major binding receptor for unopsonized particles and bacteria on human alveolar macrophages. *J Immunol* 2005; 175: 6058-6064.
- Bang KM, Attfield MD, Wood JM, Syamlal G: National trends in silicosis mortality in the United States, 1981-2004. *Am J Ind Med* 2008; 51:633-639.

- Barrett EG, Johnston C, Oberdorster G, Finkelstein JN: Silica-induced chemokine expression in alveolar type II cells is mediated by TNF-alpha-induced oxidant stress. *Am J Physiol* 1999; 276: L979-988.
- Boulanger MJ, Chow DC, Brevnova EE, Garcia KC: Hexameric structure and assembly of the interleukin-6/IL-6 alpha-receptor/gp130 complex. *Science* 2003; 300:2101-2104.
- Bowden DH: Macrophages, dust, and pulmonary diseases. *Exp Lung Res* 1987; 12: 89-107.
- Broide DH, Lotz M, Cuomo AJ, et al: Cytokines in symptomatic asthma airways. *J Allergy Clin Immunol* 1992;89:958-967.
- Castranova V: Signaling pathways controlling the production of inflammatory mediators in response to crystalline silica exposure: role of reactive oxygen/nitrogen species. *Free Radic Biol Med* 2004; 37:916-925.
- Chen F, Shi X: NF-kappaB, a pivotal transcription factor in silica-induced diseases. *Mol Cell Biochem* 2002; 234-235:169-176.
- Claudio E, Segade F, Wrobel K, Ramos S, Lazo PS. Activation of murine macrophages by silica particles in vitro is a process independent of silica-induced cell death. *Am J Respir Cell Mol Biol* 1995; 13:547-554.
- Corsini E, Giani A, Lucchi L, et al: Resistance to acute silicosis in senescent rats: role of alveolar macrophages. *Chem Res Toxicol* 2003; 16: 1520-1527.
- Driscoll KE, Hassenbein DG, Carter J, et al: Macrophage inflammatory proteins 1 and 2: expression by rat alveolar macrophages, fibroblasts, and epithelial cells and in rat lung after mineral dust exposure. *Am J Respir Cell Mol Biol* 1993;8: 311-318.
- Driscoll KE, Lindenschmidt RC, Maurer JK, Higgins JM, Ridder G: Pulmonary response to silica or titanium dioxide: inflammatory cells, alveolar macrophage-derived cytokines, and histopathology. *Am J Respir Cell Mol Biol* 1990; 2: 381-390.
- Duits AJ, Jainandunsing SM, van de Winkel JG, Capel PJ: Selective enhancement of Leu-CAM expression by interleukin 6 during differentiation of human promonocytic U937 cells. *Scand J Immunol* 1991; 33:151-159.
- Elomaa O, Kangas M, Sahlberg C, et al: Cloning of a novel bacteria-binding receptor structurally related to scavenger receptors and expressed in a subset of macrophages. *Cell* 1995; 80: 603-609.
- Elomaa O, Sankala M, Pikkarainen T, et al: Structure of the human macrophage MARCO receptor and characterization of its bacteria-binding region. *J Biol Chem* 1998; 273: 4530-4538.
- Fukuda T, Fukushima Y, Numao T, et al: Role of interleukin-4 and vascular cell adhesion molecule-1 in selective eosinophil migration into the airways in allergic asthma. *Am J Respir Cell Mol Biol* 1996;14:84-94.
- Grehardsson G:2002. the end of silicosis in Sweden- a triumph for occupational hygiene engineering. Available: [http:// www. ufa. se/ publikationer.OSHD4/3silicos.html](http://www.ufa.se/publikationer.OSHD4/3silicos.html)[accessed5 Feb.2010].
- Griffith TS, Brunner T, Fletcher SM, Green DR, Ferguson TA: Fas ligand-induced apoptosis as a mechanism of immune privilege. *Science* 1995; 270: 1189-1192.
- Hamilton RF, Jr., Thakur SA, Holian A: Silica binding and toxicity in alveolar macrophages. *Free Radic Biol Med* 2008; 44:1246-1258.
- Hamilton RF, Jr., Thakur SA, Mayfair JK, Holian A: MARCO mediates silica uptake and toxicity in alveolar macrophages from C57BL/6 mice. *J Biol Chem* 2006; 281: 34218-34226.
- Hilton DJ, Zhang JG, Metcalf D, et al: Cloning and characterization of a binding subunit of the interleukin 13 receptor that is also a component of the interleukin 4 receptor. *Proc Natl Acad Sci U S A* 1996; 93:497-501.
- Hubbard AK, Timblin CR, Shukla A, Rincon M, Mossman BT: Activation of NF-kappaB-dependent gene expression by silica in lungs of luciferase reporter mice. *Am J Physiol Lung Cell Mol Physiol* 2002; 282:L968-975.
- Jagirdar J, Begin R, Dufresne A, et al: Transforming growth factor-beta (TGF-beta) in silicosis. *Am J Respir Crit Care Med* 1996; 154:1076-1081.
- Kangas M, Brannstrom A, Elomaa O, et al: Structure and chromosomal localization of the human and murine genes for the macrophage MARCO receptor. *Genomics* 1999; 58: 82-89.
- Kishimoto T, Akira S, Narazaki M, Taga T: Interleukin-6 family of cytokines and gp130. *Blood* 1995;86:1243-1254.
- Lehnert BE, Valdez YE, Tietjen GL: Alveolar macrophage-particle relationships during lung clearance. *Am J Respir Cell Mol Biol* 1989; 1: 145-154.
- Lehtiw S, Goldstein G: 2002. Elimination of silicosis from the world. OSHA Dev4:31- 33. Available: [http:// www. ufa. se/ publikationer. OSHD4/5elimination.html](http://www.ufa.se/publikationer.OSHD4/5elimination.html). [Accessed 8 Feb 2010].
- Lenardo M, Chan KM, Hornung F, et al: Mature T lymphocyte apoptosis--immune regulation in a dynamic and unpredictable antigenic environment. *Annu Rev Immunol* 1999;17: 221-253.
- Lukacs NW, Hogaboam C, Chensue SW, Blease K, Kunkel SL: Type 1/type 2 cytokine paradigm and the progression of pulmonary fibrosis. *Chest* 2001; 120:5S-8S.
- Lutticken C, Wegenka UM, Yuan J, et al: Association of transcription factor APRF and protein kinase Jak1 with the interleukin-6 signal transducer gp130. *Science* 1994; 263: 89-92.
- Marini M, Vittori E, Hollemborg J, Mattoli S: Expression of the potent inflammatory cytokines, granulocyte-macrophage-colony-stimulating factor and interleukin-6 and interleukin-8, in bronchial epithelial cells of patients with asthma. *J Allergy Clin Immunol* 1992;89:1001-1009.
- Merchant RK, Peterson MW, Hunninghake GW: Silica directly increases permeability of alveolar epithelial cells. *J Appl Physiol* 1990; 68:1354-1359.
- Migliaccio CT, Buford MC, Jessop F, Holian A: The IL-4R α pathway in macrophages and its potential role in silica-induced pulmonary fibrosis. *J Leukoc Biol* 2008; 83: 630-639.
- Mossman BT, Churg A: Mechanisms in the pathogenesis of asbestosis and silicosis. *Am J Respir Crit Care Med* 1998; 157: 1666-1680.
- Nagata S: Fas ligand-induced apoptosis. *Annu Rev Genet* 1999; 33: 29-55.
- Nakajima K, Matsuda T, Fujitani Y, et al: Signal transduction through IL-6 receptor: involvement of multiple protein kinases, stat factors, and a novel H7-sensitive pathway. *Ann N Y Acad Sci* 1995; 762: 55-70.
- Ortiz LA, Lasky J, Lungarella G, et al: Upregulation of the p75 but not the p55 TNF-alpha receptor mRNA after silica and bleomycin exposure and protection from lung injury in double receptor knockout mice. *Am J Respir Cell Mol Biol* 1999; 20: 825-833.
- Otsuki T, Sakaguchi H, Tomokuni A, et al: Detection of alternatively spliced variant messages of Fas gene and mutational screening of Fas and Fas ligand coding regions in peripheral blood mononuclear cells derived from silicosis patients. *Immunol Lett* 2000; 72:137-143.
- Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP: The pathophysiologic roles of interleukin-6 in human disease. *Ann Intern Med* 1998;128:127-137.
- Piguet, P. F., and Vesin, C: Treatment by human recombinant soluble TNF receptor of pulmonary fibrosis induced by bleomycin or silica in mice. *Eur. Respir. J.* 1994; 7, 515-518.
- Piguet, P. F., Collart, M. A., Grau, G. E., Sappino, A. P., and Vassalli, P: Requirement of tumour necrosis factor for development of silica induced pulmonary fibrosis. *Nature* 1990; 344, 245-247.
- Pryhuber GS, Huyck HL, Baggs R, Oberdorster G, Finkelstein JN: Induction of chemokines by low-dose intratracheal silica is reduced in TNFR I (p55) null mice. *Toxicol Sci* 2003;72: 150-157.
- Qiu Z, Fujimura M, Kurashima K, Nakao S, Mukaida N: Enhanced airway inflammation and decreased subepithelial fibrosis in interleukin 6-deficient mice following chronic exposure to aerosolized antigen. *Clin Exp Allergy* 2004; 34:1321-1328.
- Sempowski GD, Derdak S, Phipps RP: Interleukin-4 and interferon-gamma discordantly regulate collagen biosynthesis by functionally distinct lung fibroblast subsets. *J Cell Physiol* 1996;167:290-296.
- Stahl N, Boulton TG, Farruggella T, et al: Association and activation of Jak-Tyk kinases by CNTF-LIF-OSM-IL-6 beta receptor components. *Science* 1994;263:92-95.

Szczeklik J, Trojan J, Kopinski P, et al: [Apoptosis of bronchoalveolar lavage lymphocytes (L-BAL) in pneumoconiosis]. *Przegl Lek* 2004; 61: 235-240.

Thakur SA, Beamer CA, Migliaccio CT, Holian A: Critical role of MARCO in crystalline silica-induced pulmonary inflammation. *Toxicol Sci* 2009;108:462-471.

Thakur SA, Hamilton RF, Jr., Holian A: Role of scavenger receptor a family in lung inflammation from exposure to environmental particles. *J Immunotoxicol* 2008; 5: 151-157.

Tripathi SS, Mishra V, Shukla M, et al: IL-6 receptor-mediated lung Th2 cytokine networking in silica-induced pulmonary fibrosis. *Arch Toxicol* 2010; 84: 947-955.

Vanhee D, Gosset P, Boitelle A, Wallaert B, Tonnel AB: Cytokines and cytokine network in silicosis and coal workers' pneumoconiosis. *Eur Respir J* 1995; 8: 834-842.

Wagner GR: 1996. Screening and surveillance of workers exposed to mineral dusts, Geneva, WHO. ISBN 92-4-154498-8.

Warheit DB, Hansen JF, Yuen IS, et al: Inhalation of high concentrations of low toxicity dusts in rats results in impaired pulmonary clearance mechanisms and persistent inflammation. *Toxicol Appl Pharmacol* 1997;145: 10-22.

Webb DC, McKenzie AN, Foster PS: Expression of the Ym2 lectin-binding protein is dependent on interleukin (IL)-4 and IL-13 signal transduction: identification of a novel allergy-associated protein. *J Biol Chem* 2001; 276: 41969-41976.

Williamson BJ, Pastiroff S, Cressey G: Piezoelectric properties of quartz and cristobalite airborne particulates as a cause of adverse health effects. *Atmospheric Environment* 2001;35: 3539-3542.

Yokoyama A, Kohno N, Fujino S, et al: Circulating interleukin-6 levels in patients with bronchial asthma. *Am J Respir Crit Care Med* 1995;151: 1354-1358.

Zhu Z, Homer RJ, Wang Z, et al: Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production. *J Clin Invest* 1999;103: 779-788.