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Cytokine polymorphisms in silicosis and other pneumoconioses

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Abstract

Silicosis and coal workers' pneumoconiosis are complex multifactorial lung diseases whose etiopathogenesis are not well defined. It is generally accepted that fibrotic lung disorders are mediated by macrophage-derived cytokines and growth factors. There is evidence showing a crucial role for tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) in inflammation caused by silica dust and in the transition from simple to progressive massive fibrosis. In this review we discuss genetic polymorphisms responsible for regulating the production of these proinflammatory cytokines and their role in modifying silicosis severity. (Mol Cell Biochem **234/235**: 219–224, 2002)

Key words: silicosis, pneumoconiosis, cytokines, polymorphism, TNF-α

Introduction

Among interstitial lung disorders, silicosis and coal workers' pneumoconiosis (CWP) are the most widespread fibrotic lung diseases. Silicosis, very rarely an isolated form of pneumoconiosis in coal workers, is a chronic fibrosing disease of the lungs produced by prolonged and extensive exposure to free crystalline silica. When workers inhale silica, the lung tissue reacts by developing fibrotic nodules and scarring around the trapped silica particles. This pulmonary fibrotic condition is called silicosis and usually occurs against a background of a simple nodular or macular CWP. Workers in mines, foundries, blasting operations, stone, clay and glass manufacturing encounter silica [1, 2]. In the United States, between 1979 and 1996, 2,694 deaths were attributed to silicosis. About 1.6 million workers are believed to have been exposed to silica dust, and almost 60,000 are expected to suffer from some degree of silicosis. CWP, also known as black lung disease, is caused by inhaling coal mine dust. When the disease progresses from simple to complicated pneumoconiosis, the condition is called progressive massive fibrosis. An estimated 4.5% of coal miners are affected and about 0.2% have scarring on the lungs, the most severe form of the disease. Between 1979 and 1996, 14,156 deaths were attributed to black lung disease [2, 3].

Although their pathophysiology has not been fully understood, several lines of evidence suggest the participation of cytokines produced by alveolar macrophages (AM), at least in the initiation of the alveolitis. The AM is a critically important cell playing a prominent role in lung inflammation via the production of a large panel of mediators including cytokines, reactive oxygen species, enzymes and arachidonic acid metabolites [4, 5].

Inflammatory cytokines as candidate genes for fibrotic lung diseases

Cytokines play key roles in immune responses, inflammation and fibrosis. The cytokines receiving the most attention to date, in relation to pulmonary diseases, include IL-1, TNF-

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α, platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), insulin-like growth factor I (IGF-I), and interleukin-6 (IL-6) [6–9]. Experimental animal and clinical studies reveal that TNF-α and IL-1 are important in regulating fibrotic mediators in silicosis. In this respect, increased expression of inflammatory cytokines corresponds to pathological changes in lungs of silicotic rodents [10–14]. A major role of TNF-α in pulmonary fibrosis is supported by evidence obtained from TNF-α deficient mice, which are resistant to developing fibrosis from silica [15,16]. In humans, the local release of IL-1 and TNF-α has been shown to coincide with pathogenesis of the disease [17, 18]. Coal mine dust-stimulated release of TNF-α from peripheral blood monocytes (PBM) was also increased in subjects with pneumoconiosis [19–21] while higher levels of spontaneous TNF-α and IL-1 secretion by AMs were observed in patients with CWP [22]. In addition, elevated mRNA levels of TNF-α have been observed in lungs of subjects with pneumoconiosis [23]. These results indicate that AMs are involved in chronic lung inflammatory reactions to mineral dusts, partly by way of cytokine secretion. Moreover, cytokine secretion by AMs was suggested to be an early event in response to mineral dust exposure.

Associations between disease and IL-1 and TNF-α polymorphisms

Multifactorial diseases involve complex interactions among multiple genes and environmental factors. Susceptibility depends on both intrinsic features of the host and the influence of environmental factors [24]. Genetic factors such as polymorphisms are usually not, by themselves, sufficient for most diseases but modify the extent or severity of the disease after it has been initiated. As with other multifactorial diseases, there is a wide inter-individual variability of susceptibility to silicosis. The role of genetic and environmental or physiological factors as disease modifiers may be described as shown in Fig. 1. This pattern is similar to the model of clinical expression of adult periodontitis outlined by Kornman *et al*. [25].

Polymorphisms in cytokine genes have been reported to contribute to the recognized stable inter-individual variation in the level of cytokine production rates [26–28]. Inter-individual differences in spontaneous as well as stimulated production of IL-1 and TNF-α support the possibility that silicosis and pneumoconiosis severity are related to the genetic propensity of the host to produce these proteins. At the IL-1 and TNF loci, some allelic variants have been found to be significantly over-represented in inflammatory diseases. These variations affect the level of TNF-α expression in response to various stimuli. In humans the gene encoding for TNF-α is located on chromosome 6 between HLA-B and DR, within the class III region of the major histocompatibility complex, and is a candidate gene for autoimmune and inflammatory diseases [29, 30]. Two SNPs, at positions –308 and –238 in the promoter region, [30, 31] are associated with a variety of immune and inflammatory diseases, such as CWP, malaria, leishmaniasis, celiac disease, chronic bronchitis, psoriasis and systemic lupus erythematosus [32–38]. Due to the high degree of linkage disequilibrium across the MHC, TNF-α expression may depend on polymorphisms in the TNF-α promoter region or a linkage association with the HLA genotype [31, 39]. Therefore, it is difficult to determine which genes on a haplotype are important in the etiology of a disease. The –308 variant of TNF-α is reported to be associated with the HLA A1, B8, DR3, DR4 and the DQ2 haplotypes. DR2 positive genotypes have been reported to produce low levels of TNF-α whereas the DR3 and DR4 genotypes produce high levels [30, 40]. Therefore, the increased production of TNF-α could contribute to the increased incidence of autoimmune diseases observed in individuals with an HLA A1, B8 and DR3 haplotypes [41].

Polymorphisms within the human IL-1 gene cluster on chromosome 2 have been associated with several chronic inflammatory diseases [42]. The minor variant of the IL-1RA VNTR in linkage disequlibrium with exon 2 (+2018) has been associated with systemic lupus erythematosus, ulcerative colitis, lichen sclerosis and alopecia areata [43–46]. Two variants in the IL-1α gene at sites –889 and +4845 are over-represented in juvenile rheumatoid arthritis and chronic polyarthritis [47, 48]. The IL-1β (+3953) variant has been found to be prevalent in severe periodonditis and psoriasis [25, 49].

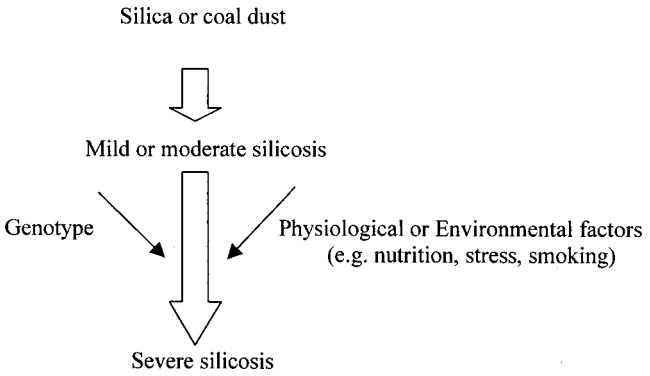

Fig. 1. In the gene by environmental interaction in a biological sense, silica or coal dust are the causal elements producing disease, but specific genotypes and physiological or environmental factors may modify the clinical expression of disease after it has been initiated.

IL-1 and TNF genotypes in silicosis and CWP

In caucasian patients with silicosis, the frequency of HLA-B7 was found to be lower than that in dust-exposed and non-exposed referents and the highest risk of developing severe fibrosis was found to be associated with the HLA-Aw19-B18 haplotype [50, 51]. Immunogenetic analysis revealed that susceptibility to silicosis is associated with HLA-Bw54 in the Japanese population, suggesting that a TNF-α allele, in linkage disequilibrium with this haplotype, might predispose individuals to silicosis. The major gene for silicosis was also reported to be mapped near the HLA-B locus [52]. The frequency of DR8 was elevated in German coal miners with CWP, whereas the frequency of DR1 and DR52 was reduced in miners without CWP [53]. In another study, an increased presence of the –308 variant in the TNF-α promoter was reported in ex-coal miners with mild CWP [38].

In most chronic inflammatory diseases, whatever the role of environmental factors, there are genetic components which cannot be attributed to those linked to the MHC [54]. In view of the genetic findings and the chronic inflammatory nature of silicosis, we investigated whether polymorphisms in the IL-1 and TNF-α genes are associated with the incidence and/or severity of this disease. In this study, all the subjects were selected from a total of 6580 autopsy cases submitted to the National Coal Workers' Autopsy Study from 1972–1996. From these subjects, a random sample of 325 cases was selected and genotyped for at least one of the polymorphisms. Additional 164 autopsy subjects without any evidence of pulmonary disease were defined as controls. Cases with pulmonary silicosis were reviewed and graded according to the criteria and schema developed by a joint committee of the National Institute for Occupational Safety and Health (NIOSH) and College of American Pathologists. Lesions were graded subjectively into three grades of severity; mild, moderate and severe, based on profusion and size of lesions in the sections. All individuals included in the study were Caucasian, males and worked as underground coal miners. Table 1 summarizes the distribution of age, smoking status and years of exposure by disease status.

The polymorphisms that were investigated, distribution of genotypes and allelic frequencies are listed in Table 2. Subjects with severe silicosis were compared to subjects with moderate disease and to subjects with no silicosis. Odds ratios were calculated using a logistic regression model after adjusting for years of occupational exposure. The odds ratio represents the odds of being a case (i.e. proportion of cases divided by proportion of controls) in subjects with the polymorphism divided by the odds of being a case in subjects without the polymorphism. We observed a strong association between silicosis and the TNF-α (–238) variant, as the frequency of this allele were significantly reduced in moderate disease and significantly predictive of severe disease (adjusted odds ratio 0.5 and 4.0, respectively). This implies that individuals with the TNF-α (–238) variant are predisposed to more rapid development of severe silicosis, which would account for the apparently protective effect on moderate outcomes since those individuals are progressing past moderate status with a higher probability. Regardless of disease severity, the TNF-α (–308) variant showed an increased risk for both moderate and severe disease (adjusted odds ratios of 3.6 and 1.6, respectively). The distribution of the minor variant did not show a consistent relationship with disease since the association was confounded by occupational exposure [55].

The proportion of the IL-1RA (+2018) allele 2 genotype was increased in miners with silicosis (0.27) compared to controls (0.16) [56]. This minor variant was significantly increased in miners with both moderate and severe silicosis suggesting that this variant affects susceptibility to silicosis rather than severity. Although there was no association with the IL-1β variant, an allelic association between IL-1RA and IL-1α was found ($p = 0.04$) [55]. This may also represent a susceptibility factor for silicosis as the IL-1/IL-1RA ratio is important in the regulation of inflammatory processes [57].

Much more is known about the environmental causes of silicosis than about the genes influencing disease. It is theoretically possible that a gene might have no independent effect itself on silicosis occurrence but in combination with another gene or a specific environmental exposure confer an increased risk. In this respect, examination of two-way gene-gene interactions provides insight into the contribution of these SNPs and silicosis. After adjusting for exposure, while the IL-1RA and TNF-α (–308) interaction showed a strong independent association between each SNP and moderate disease, the presence of both variants led to much higher odds

Table 1. Age, smoking status and years of exposure by disease status

Population	Number of patient	Mean (range; S.D.)		
		Age	Years smoking	Years exposure
Controls	164	63.2 (50–87; 8.0)	20.4 (0–50; 16.4)	21.3 (1–58; 13.3)
Moderate	140	66.9 (27–87; 9.2)	20.5 (0–70; 19.1)	34.4 (10–52; 10.1)
Severe	185	68.7 (39–93; 8.8)	17.9 (0–60; 18.4)	34.2 (1–55; 11.3)
Overall	489	66.3 (27–93; 9.0)	19.5 (0–70; 18.0)	29.9 (1–58; 13.2)

Adapted from ref. [55].

Table 2. Distribution of genotypes and allele frequencies

Disease status	Normal: 1/1 alleles	Carrier:1/2 or 2/2	Allele 2 frequency	AdjustedOR (CI)**
TNF-α (–308)[a]				
Controls	75	79	0.27	1.00
Moderate	40	97	0.37	3.59 (2.0–6.4)
Severe	83	74	0.24	1.61 (0.9–2.8)
All Silicotic*	123	171	0.30	2.25 (1.4–3.6)
TNF-aα (–238)[a]				
Controls	87	73	0.24	1.00
Moderate	91	41	0.16	0.52 (0.3–0.9)
Severe	42	141	0.40	4.00 (2.4–6.8)
All Silicotic	133	182	0.30	1.59 (1.0–2.5)
IL-1RA (+2018)[a]				
Controls	113	44	0.16	1.00
Moderate 54	60	0.35	2.54 (1.4–4.5)	
Severe 95	65	0.22	2.01 (1.2–3.4)	
All Silicotic	149	125	0.27	2.15 (1.3–3.5)
IL-1α (+4845)				
Controls	125	31	0.10	1.00
Moderate 111	21	0.08	0.47 (0.2–0.9)	
Severe 113	42	0.15	0.90 (0.5–1.6)	
All Silicotic	224	63	0.12	0.76 (0.4–1.3)
IL-1β (+3953)				
Controls	43	95	0.36	1.00
Moderate 35	75	0.40	0.8 (0.5–1.6)	
Severe	55	88	0.36	0.72 (0.4–1.3)
All Silicotic	90	163	0.38	0.75 (0.4–1.2)

[a]Significantly associated with moderate, severe, and overall disease ($p < 0.05$). *Represents total population studied with silicosis. **Odds ratio (95% confidence limits) adjusted for exposure with logistic regression. Adapted from ref. [55].

for severe disease. Three-way interaction analysis between each gene-gene interaction and exposure led to only marginally significant associations. The general pattern demonstrated in each of these interactions is exemplified by the IL-1α and TNF-α (–308) association ($p = 0.05$) [55]. The prevalence of silicosis increases with increasing exposure, except in the case where both minor variants are present. For the group in which subjects are an allele 2 carrier in both polymorphisms, there is little or no effect of increasing exposure and this group has the highest proportion of moderate and severe cases for those exposed less than 30 years.

In conclusion, polymorphisms in the genes for IL-1 and TNF-α show both independent and interrelated effects on susceptibility and severity of silicosis in underground miners. These results indicate that the risk of a person acquiring or developing an inflammatory disease is influenced not only by exposure levels, but also by genetic polymorphisms of the cytokine system. Future studies in this area and identification of functional polymorphisms for other candidate genes will allow for a better estimate of determining susceptible populations and will improve human risk assessment.

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