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Chemokines involved in the early inflammatory response and in pro-tumoral activity in asbestos-exposed workers from an Italian coastal area with territorial clusters of pleural malignant mesothelioma

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ABSTRACT

Objectives: Immune mediators are likely to be relevant for the biological response to asbestos exposure. The aim of this study was to investigate the association between immune mediators involved in inflammation, cell survival and angiogenesis, and asbestos-related diseases in workers from a coastal area of North-East Italy with a high incidence of pleural malignant mesothelioma (PMM).
Materials and methods: A selected custom set of 12 soluble mediators was evaluated with a Luminex platform in sera, pleural fluid and mesothelioma biopsies from 123 asbestos-exposed workers (38 free from pleural-pulmonary disorders, 46 with non-malignant asbestos diseases, 39 with PMM) and in sera from 33 healthy controls from the same territorial area.
Results: Increased immune mediator concentrations were observed in the sera of the asbestos-exposed workers compared to controls for human fibroblast growth factor (FGF-b), vascular endothelial growth factor (VEGF), CCL5 (RANTES), CXCL10 (IP-10), CLEC11A (SCGF-b), CCL27 (CTACK), CCL11 (EOTAXIN), IL-5 and IL-6 ($p < 0.001$). The chemokines IP-10 and RANTES were associated with the severity of asbestos-related diseases. In the workers with PMM, the immune proteins secreted by mesothelioma biopsies showed detectable levels of RANTES, VEGF, and IP-10. In the same workers with PMM, a significant relationship between serum and pleural fluid concentrations was found for RANTES alone.
Conclusions: Occupational exposure to asbestos seems to drive the production of specific growth factors dually involved in the early inflammatory response and in pro-tumoral activity before clinical evidence of related disorders, suggesting that their over-expression may precede the onset of asbestos-related diseases. These findings suggest that some chemokines may have a prognostic role in the progression of asbestos-related diseases and could be used for the health surveillance of either workers with an occupational history of asbestos exposure or patients affected by non-malignant asbestos-related diseases.

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1. Introduction

Exposure to asbestos and the nature of the inhaled fibers are associated with a high risk of developing lung and mesothelial diseases including pleural malignant mesothelioma (PMM) [1,2].

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In mesothelial and lung epithelial cells, asbestos fibers initiate signaling and survival pathways which are often up-regulated in PMM and contribute to tumor pathogenesis [3]. Asbestos fibers deposited in the distal regions of the respiratory system cause early and sustained inflammation. The inflammatory process is sustained by interaction of the fibers with epithelial cells and alveolar macrophages which, in turn, may release chemical mediators up-regulating these pathways. The mentioned pathways may be activated by a direct interplay of asbestos fibers with receptors on the cell surface and with integrins or via elaboration of ROS generated catalytically on the fiber surface or after frustrated phagocytosis [4]. In addition, an increase in the expression of genes encoding cytokines/chemokines such as IL-8 and their receptors or ligands such as CXCL2 and CXCL3 is promoted, suggesting that mesothelial cells may orchestrate leukocyte chemotaxis and trafficking and pleural inflammation [5–8].

Recent research has reported that cancer, including mesothelioma, subvert the normal pathway of inflammatory proteins, which become crucial constituents of the tumor microenvironment and influence its development and metastasis. Specifically, the supernatants of asbestos-exposed mesothelioma cell lines contained higher levels of vascular endothelial growth factor (VEGF) than the supernatants of unstimulated normal mesothelial cells, and such differences were also noticed for fibroblast growth factor (FGF). Similarly, the serum levels of both proteins were found to be significantly higher in mesothelioma patients than in controls or patients with other malignancies [9].

TNF-α release and cooperation to the activation of the Ras/MAPK/NF-kB pathway is one of the described mechanisms by which tumor cell-macrophage crosstalk may enhance tumor growth and influence the over-expression of both CC and CXC chemokines in amplifying paracrine signaling loops [10,11]. Nevertheless, the important contribution of IL-1b and TNF-α to mesothelial cell malignant transformation may be partially due to activation of AP-1 – or NF-kB – dependent gene expression [12].

The chronic inflammatory response to the asbestos cellular damage probably perpetrated by the Nod-like receptor protein 3 (NLRP3) inflammasome [13,14] represents an important aspect of the pulmonary microenvironment, characterized by a strong interplay between high levels of soluble mediators, immune cells, airway epithelial cell proliferation and angiogenesis [3,15–17]. Notably, independently of asbestos fiber deposition, an array of pro-angiogenic molecules, growth factors and pro-inflammatory cytokines has been detected during the abnormal growth and differentiation of mesothelial cells in visceral pleura. It is plausible that such changes, which precede tumor development, may be linked causally to PMM [18–20].

Malignant pleural mesothelioma is a clinically aggressive tumor and no single-modality therapy has proven effective in curing it, presumably because of the multiplicity of survival and chemoresistance pathways in this tumor. PMM seems to respond to immunotherapy and patients are known to mount an anti-tumor immune response [21]. Careful surveillance of patients exposed to asbestos is a key issue in controlling the development of asbestos-associated diseases and the identification of healthy, asymptomatic persons exposed to asbestos could be an important result.

Since the production of immune mediators is likely to be relevant for the biological response to asbestos exposure and PMM seems to be responsive to immunotherapy, we undertook the present study with the aim of investigating the associations between asbestos exposure, asbestos-related diseases and candidate immune mediators involved in multiple cellular pathways affecting the inflammatory response, cell survival and angiogenesis [22–25], in a cohort of workers with a history of occupational asbestos exposure in a coastal area of North-East Italy with a high incidence of PMM [26].

2. Materials and methods

2.1. Study population

For this cross-sectional study, 123 male workers with a history of definite occupational exposure to asbestos (amphibole types) were consecutively enrolled during either a health surveillance survey (n = 84) or during hospital attendance for diagnostic procedures at a Thoracic Surgery Unit (n = 39). These subjects had a past occupational history of asbestos use in dockyards (asbestos handling and transport) and shipyards (naval construction and/or repair activities) located in a coastal area of the Provinces of Gorizia and Trieste in North-East Italy with a high incidence of PMM. In this geographical area, the average annual incidences of PMM among men in the period 1995–2013 varied from 13.4 (per 100,000) in the Province of Trieste to 14.9 (per 100,000) in the Province of Gorizia, about four times higher than the corresponding Italian incidence rates [27,28]. It was documented that more than 80% of the deaths for PMM in the two Provinces could be attributed to definite, probable or possible occupational exposures to asbestos [28]. Occupational exposures to asbestos were ascertained by means of a structured questionnaire according to the standardized guidelines provided by the National Mesothelioma Register (ReNaM) [29]. Duration of asbestos exposure was expressed in terms of years of employment in jobs known to be associated with the use and handling of asbestos materials. Additional information on asbestos exposure was recovered from the records of the local Mesothelioma Register. The cohort of asbestos-exposed workers examined during the health surveillance survey included 38 subjects free from any pleural or lung disorders (Healthy workers) and 46 workers suffering from non-malignant asbestos diseases (pleural plaques or diffuse pleural thickening and/or pulmonary fibrosis) (NMAD workers). The diagnosis of NMAD was based on medical history, a clinical examination, radiological investigations (chest radiograph, CT scan), and spirometry. The 39 asbestos-exposed workers recruited at the hospital were affected by PMM (PMM workers). The histological diagnosis of tumor was based on surgical pleural biopsy and/or pleural fluid (PF) examination in accordance with the World Health Organization criteria [30,31]. In a selected group of patients (16/39), both PF and pleural biopsy were available for each patient. The histotypes of PMM were classified as epithelioid and biphasic in 31 and 8 subjects, respectively.

Matching PF and mesothelioma biopsies (epithelioid histotype) were available for 16 out of the 39 PMM workers at the time of diagnosis. Clinical data and biological samples including serum, PF and mesothelioma biopsies were collected after written informed consent in accordance with the principles outlined in the Declaration of Helsinki (2014).

For the PMM workers, the study enrolment criteria at the time of sampling included: no pre-operative chemotherapy and radiotherapy, no associated neoplasia, no smokers and no kind of diagnostic workup or treatment.

A control group comprising 33 healthy immunocompetent males with no occupational exposure to asbestos was selected on the basis of the following characteristics: no smoking subjects, no hospitalization in the past two years, no chronic systemic medication, no hematological evidence of autoimmune diseases, and no findings of lung dysfunction at the time of enrollment.

The study was approved by the local Ethics Committee of the University Hospital “Ospedali Riuniti di Trieste”, Trieste, Italy.

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