Human Chitotriosidase in Lung and Liver Fibrosis

Elena Bargagli1*, Massimo Pistolesi1, Elisabetta Rosi1, Antje Prasse2, and Luca Voltolini3

1Section of Respiratory Medicine, Department of Clinical and Experimental Medicine; Department of Clinical and Experimental Biomedical Sciences, University of Florence, Florence, Italy
2Hannover Medical School, Clinic for Pneumology, Hannover, Germany
3Thoracic Surgery Unit, University Hospital Careggi, Largo Brambilla, 1, 50134, Florence, Italy

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*Corresponding author: Elena Bargagli, Section of Respiratory Medicine, Department of Clinical and Experimental Medicine; Department of Clinical and Experimental Biomedical Sciences, University of Florence, Florence, Italy, E-mail: bargagli2@gmail.com.

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Abstract

Sarcoidosis is a multi-organ granulomatous disease associated with macrophage and T-lymphocyte activation and migration into affected organs [1,2]. The clinical expression, natural history and prognosis of sarcoidosis are unpredictable and no reliable indicators of clinical outcome are available. Proposed biomarkers include cytokines, chemokines and macrophage- or lymphocyte derived mediators but there is no single reliable biomarker with demonstrated unequivocal prognostic value [1–6]. In the last years different research groups reported a pathogenic role of chitinases as immunomodulatory molecules involved in macrophages and T-cell proliferation and innate immune system regulation in sarcoidosis [7–11]. Twelve years ago an increase in chitotriosidase concentrations was firstly documented in serum and BAL from progressive advanced sarcoidosis with fibrotic lung involvement (normal values < 18 nmol/h/ml in serum and < 2 nmol/h/mg in BAL) [4]. Enzyme levels were reported significantly higher in patients with advanced lung fibrotic involvement (stage 3 and 4) than in early stages of sarcoidosis (stage 0 and 1) and chitotriosidase has been proposed as a biomarker of disease severity correlated with radiological stage and serum levels of IL2r and ACE [6,11].

Chitotriosidase involvement in the pathogenesis of interstitial lung diseases and airway remodeling is a major research topic. Macrophages release chitotriosidase after stimulation with interferon gamma (IFN-γ), tumor necrosis factor (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF) that interacts with TGF-β1, up-regulating fibroblast TGF-β receptor 1 and 2 expression and increasing TGF-β-induced signaling [6,9]. Chitinase 1 interferes with innate and adaptive immunity, participating in defense against pathogens containing chitin [4]. A major function of CHIT1 is to degrade the chitin present in infectious microorganisms such as fungi, parasites and house dust mites [5]. Interestingly, GRADS (a study presented for the first time at the ATS Conference) reported that microbiome play a role in sarcoidosis susceptibility and development, suggesting that infective agents (including chitin-containing pathogens such as fungi) may have pathogenic significance in this disease. In this context, chitotriosidase could be directly involved in the pathogenesis of sarcoidosis by virtue of its pleiotropic effects in infectious and non-infectious inflammation as well as in immune responses to pathogens with and without chitin [7]. Moreover, it has been demonstrated that chitotriosidase induces overexpression of profibrotic cytokines in sarcoidosis as well as in hepatic fibrotic diseases with similar pathways. In the sarcoidosis session of the ATS conference, a recurrent parallel was underlined between liver fibrosis and lung fibrosis associated with sarcoidosis. Common pathogenic mechanisms and mediators contributed to liver fibrosis as well as lung fibrosis secondary to sarcoidosis. For example, IL17 and T helper 17 were proposed as mediators of sarcoidosis immunopathogenesis at the conference as well as in an interesting manuscript recently published in the AJRCCM [8]. These pathways have been associated with development of fibrosis in patients with chronic fibrotic liver diseases [8]. Th 17-mediated immune response is regarded as a bioindicator of liver fibrotic degeneration in patients with hepatitis B and cirrhosis and has also been associated with chronic sarcoidosis with lung fibrosis phenotype. Another common mediator proves to be chitinase 1, over expressed in liver and pulmonary fibrosis associated with sarcoidosis [9]. Interestingly, these pathways common to liver and lung fibrosis do not seem involved in all interstitial lung diseases. Several mediators commonly over expressed in stage 4 sarcoidosis and in patients with chronic hepatic fibrosis are not increased in idiopathic pulmonary fibrosis, where indeed no significant involvement of chitotriosidase, Th17 immune response or microfibril associated glycoprotein 4 (MFP4) has been demonstrated [10]. Chitinase 1 modulates tissue remodeling processes in fibroblastic liver tissue (as well as in the lung) being produced by Kupffer cells and activated macrophages, which by activating hepatic stellate cells induce hepatic fibrosis and cirrhosis [9]. In sarcoidosis, active lung macrophages produce increased levels of chitotriosidase, facilitating granuloma formation and lung fibrotic alteration. In contrast, the production of CHIT1 proved down-regulated or not increased in other inflammatory or fibrotic diseases such as ulcerative colitis and idiopathic pulmonary fibrosis [9]. Chitinase 1 resulted to be involved in sarcoidosis and not in other diffuse fibrotic lung disorders [10]. Serum chitotriosidase could be a useful biomarker to distinguish sarcoidosis from other pulmonary and systemic diseases including idiopathic pulmonary fibrosis and pulmonary fibrosis associated with systemic sclerosis. Studies suggest that chitotriosidase could be involved in fibrogenesis of different ILD but high levels (10 folds greater than controls) are present only in sarcoidosis [11]. In pulmonary fibrosis associated with systemic sclerosis, it has been demonstrated that chitinase 1 serum levels correlated with disease severity and lung fibrotic involvement [12]. In vivo animal models of pulmonary fibrosis associated with connective tissue lung disorders it has been observed that chitotriosidase enhanced bleomycin- or IL-13-stimulated pulmonary fibrosis interacting with fibroblasts through TGF-β1 signaling [12]. Unfortunately no data is available about chitotriosidase concentrations in pneumoconiosis or fibrosis associated with rheumatoid arthritis.

Analogously to chitotriosidase, another interesting biomarker...
of sarcoidosis produced by activated macrophages and neutrophils is YKL-40 (also named human cartilage glycoprotein-39). This is a heparin and chitin-binding lectin without chitinase activity, increased in serum of almost 2/3 of sarcoidosis patients than controls [13,14]. YKL-40 concentrations in serum negatively correlated with DLC0/VA discriminating in particular sarcoidosis patients with fibrotic involvement [14].

Both chitotriosidase and YKL-40 play a role in the fibrotic remodeling occurring in interstitial and granulomatous lung disorders, as demonstrated by Cho et al. [15]. These authors suggested that chitinase 1 in particular resulted both an innate immune mediator as well as a regulator of tissue remodeling involved in fibrotic processes by the enhancement of TGF-β1 receptor expression and signaling.

Chitotriosidase serum concentration correlates with the progression or the severity of ILD, suggesting a potential use of CHI3L1 as a therapeutic target in particular in patients with pulmonary fibrosis associated with systemic sclerosis analogously to lysosomal storage disorders such as Gaucher disease [16].

Human microfibril-associated glycoprotein 4 is another protein involved in extracellular matrix remodeling and fibrosis development in patients with end stage hepatitis C. This protein is regarded as a biomarker of hepatic fibrosis, being increased in serum of these patients but not in IPF patients or BAL of bleomycin-treated mice with pulmonary fibrosis (17).

In conclusion, chitotriosidase may promote tissue repair responses associated with injury produced by adaptive Th2 responses in liver and pulmonary fibrosis associated with sarcoidosis. This enzyme is a useful biomarker and a potential therapeutic target in different inflammatory and fibrotic lung diseases. Its role has not been documented for all interstitial lung diseases, including idiopathic pulmonary fibrosis.

References


*Corresponding author: Elena Bargagli, Section of Respiratory Medicine, Department of Clinical and Experimental Medicine; Department of Clinical and Experimental Biomedical Sciences, University of Florence, Florence, Italy, E-mail: bargagli2@gmail.com.

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