

# Chitinases and lung diseases

Serap DÜRÜ, Melike YÜCEEĞE, Sadık ARDIÇ

SB Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, Ankara.

## ÖZET

### *Kitinazlar ve akciğer hastalıkları*

*İnsan vücudunda kitin olmamasına rağmen kitin ve kitinin bazı yapay substratlarını hidroliz eden kitinaz enzimleri eksprese edilmektedir. Kitinazların insandaki patofizyolojik fonksiyonları tam olarak bilinmemektedir. Son kanıtlar kitinazların immün yanıt ve inflamatuvar sistemde rol aldığını göstermektedir. Bu derlemede, kitinazların akciğer hastalıklarındaki rolünü literatür bilgileri eşliğinde tartıştık.*

**Anahtar Kelimeler:** *Kitinazlar, akciğer, immünite.*

## SUMMARY

### *Chitinases and lung diseases*

Serap DÜRÜ, Melike YÜCEEĞE, Sadık ARDIÇ

Clinic of Chest Diseases, Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey.

*Chitinase enzymes that hydrolyze chitin and some artificial substrates are expressed in human despite lacking of the endogenous chitin within the body. Chitinases pathophysiological functions within human are not fully known. Recent evidence revealed that chitinases may have role into some processes of immune responses and inflammatory system. In this review, we discuss the role of chitinases in lung diseases based on the available information from the literature.*

**Key Words:** *Chitinases, lung, immunity.*

*Tuberk Toraks 2013; 61(1): 71-75 • doi: 10.5578/lt.3773*

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### Yazışma Adresi (Address for Correspondence):

Dr. Serap DÜRÜ, SB Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği,  
ANKARA - TÜRKİYE

e-mail: akcalis@hotmail.com

Today there have been many recent studies carried out so as to identify the pathogenesis of the diseases or ameliorate the prognosis of the diseases. One of the major areas of research are those relevant to the chitinases which has been accelerated especially since 1990s.

Chitin is the most common polysaccharide after cellulose (N-acetyl-beta-D-glicosamine) in nature. Chitin is found as a structural component in the external skeleton of the arthropods, cell membrane of the fungi, the microfilar sheath of the parasitic nematodes and the wall of many of the insects' gastrointestinal channels. Chitin helps to protect the living creature internally and from environmental organisms (1,2).

There is no chitin in human body, but it is interesting that there are enzymes called chitinases which break down chitin and genes which encode those in the human body system (3). Hollak and co. were the first to detect increased chitinase (chitotriosidase) activity in the plasma in Gaucher disease in 1994 (4). The accumulation of sphingolipids causes excessive amount of chitotriosidase synthesis and secretion (100-1000 fold).

Until now, an additional seven different kinds of chitinases have been discovered along with the chitotriosidase in the chitinase family. Although chitotriosidase, acidic mammalian chitinase (AMCase) and di-N-acetyl chitinase have real chitinase activity, YKL-40 (chitinase-3 like protein 1, human cartilage glycoprotein 39) named as chitolectine, YKL-39 (chitinase 3-like protein 2, chondrocyte protein 39), ovoductine, LOC149620, SI-CLP (Stabiline-1 interacting chitinase like protein) have no enzyme activity, but they all have oligosaccharide binding capability.

The seventh of the eight genes (that belong to glycoside hydrolase 18 family) which code chitinases in human genome is located on the 1<sup>st</sup> chromosome (chitotriosidase: 1q32.1, AMCase: 1p13.2, YKL-40: 1q32.1, YKL-39: 1q13.2, Ovoductine: 1p13.2, di-N acetyl chitinase: 1p22, LOC149620: 1p13.2), while other one (SI-CLP: 11p15.5) is situated on 11<sup>th</sup> chromosome (5).

Chitotriosidase has fungistatic activity and is released from activated macrophages (6). The blood level increases in diseases such as Gaucher, Nieman Pick, Fabry, Alzheimer, bacterial and malarial diseases, atherosclerosis and sarcoidosis (2). Acidic mammalian chitinase occurs in CD<sup>+</sup> T helper two mediated immune response and furthermore it is available in lung and gastrointestinal system (7). The blood level increases in allergic inflammatory diseases such as asthma, rinit

and conjunctivitis. Di-acetylchitinase serves in the lysosomal destruction of the glycoproteins binded with chitin and asparagine (8).

YKL-40 is released from snovial fibroblasts, chondrocytes, neutrophils, smooth muscle cells, macrophages and malign tumour cells. It contributes to inflammation, angiogenesis and remodeling, cell proliferation, adesion and migration (9).

YKL-39 is released from macrophages, fibroblasts and chondrocytes. The blood level increases in inflammatory bone diseases such as osteoarthritis (10).

Ovoductine is released from ovoductal epithelial cells. It is believed to occur in development and fertilisation of embryo (11).

SI-CLP's role in health and disease is not clearly known. It is released from the endotele cells of liver, spleen, lymph node, bone marrow and tissue macrophages (9).

The chitinase activity in different lung diseases is investigated lately. In this article, we aim to highlight the role of chitinases in lung diseases.

The chitinases take place in lung diseases are shown in Table 1.

### CHITINASES and ASTHMA

Asthma is the chronic inflammatory disease of the airway. The inflammatory mediators take part in the asthma pathogenesis and structural changes such as subepithelial fibrosis and remodeling occur (12). The modulation of the inflammation in asthma is committed by Th2 lymphocytes. Th2 lymphocytes, macrophages, eosinophils and mast cells accumulate in the inflammation region in the lung following the few hours of allergen exposure. In the studies with the AMCase, its expression has been shown to increase during Th2 inflammation in the mouse lung (13). Elias and co have demonstrated interleukin (IL)-13 to regulate the production of chitin and chitin-like proteins (14). The AMCase level has been shown to increase in asthmatic patients due to the chitin in the cell membrane of fungi such as cryptococcus, aspergillus and streptomyces in the later studies (15-17). Besides, the existence of genetic polymorphism in AMCase has been shown in asthmatic patients (18). The AMCase also increases in cases with chronic sinusitis accompanying with nasal polip (19). YKL-40 is first defined as BRP-39 in mammary cancer cells in mice and it is expressed from macrophages, neutrophils and fibroblasts in the lung (20). Nucleotid polymorphism related to YKL-40 has been demonstrated in asthmatic patients and shown to be a useful mar-

**Table 1. Chitinases and lung diseases.**

	Genetic code	Released cells	Effect in lung disease	Lung disease
Chitotriosidase (CHIT1)	1q32.1	- Macrophages - Polymorphous leucocytes in healthy donors	- Inflammation	- Sarcoidosis
Acidic mammal chitinase (CHIA)	1p13.2	- Macrophages in lung - Nonproducing mucus Epithelial cells in the distal airway	- Inflammation	- Asthma - Nasal polip related with rinosynosis
YKL-40 (CHI3L1)	1q32.1	- Macrophages - Giant cell in sarcoidosis - Atherosclerotic plaques - Microglia - Malign cells - Fibroblast-like snovial cells - Chondrocytes - Vascular smooth muscle cells	- Infection - Chronic inflammation and granulom formation - Cancer spread	- Pnemonia ( <i>Streptococcus pneumoniae</i> ) - Sarcoidosis - Lung cancer (adenocarcinoma, small cell carcinoma)
YKL-39 (CHI3L2)	1q13.2	- Microglia - Fibroblast-like snovial cells - Chondrocytes in joint cartilage	- Inflammation (articular diseases)	-
SI-CLP (CHID1)	11p15.5	- Macrophages - Jurcat T cells - CD3+ T lymphocytes in peripheral blood - Raji B lymphocytes - Malign cells	- Inflammation	- Sarcoidosis
Ovuductine	1p13.2	- Ovuductal epithelial cells	- Fertilisation	

ker in the follow up of the severity of asthma (21). In a recent study, YKL-40 expression is demonstrated in the bronchial smooth muscle cells got by bronchial biopsy in asthmatic patients (22). The AMCase and YKL-40 have been considered to be usefull markers in the monitorisation of the severity of asthma (5).

#### CHITINASES and COPD

Chitinase activity has been demonstrated to be increased in the mouse model lungs with COPD recently (23). Chitinase activity was detected to be increased in bronchoalveoler lavage of smoker patients with COPD in another study (24).

YKL-40 level was increased in sputum specimens of COPD patients proportionally with the macrophage and neutrophil number which show increase with airway obstruction (25). YKL-40 is considered to take part in pulmonary inflammation and empysematous changes in smoker patients with COPD (26).

As a result, it is considered that chitinases can have roles in formation and progression of COPD and further studies are still required in this area.

#### CHITINASES and SARCOIDOSIS

Sarcoidosis is a systemic noncaseified granulomatous disease with unknown etiology and is characterised by lymphadenopathy, pulmonary infiltration, eye and skin lesions. There are studies with chitinases in sarcoidosis which is regulated by T cell mediated immunity-stimulated by cytokines and TNF alpha. Blood serum chitotriosidase activity was found to be higher in active sarcoidosis patients than inactive sarcoidosis patients. As a result, it is estimated that the defence against pathogens containing chitin could have taken part in the pathogenesis of sarcoidosis (27). Blood serum chitotriosidase was found to be higher in sarcoidosis than tuberculosis and control group (28). Increased blood serum chitotriosidase and soluble IL-12 receptor levels are shown to be useful markers in evaluating the severity of the disease in an other study in pulmonary sarcoidosis patients (29). SI-CLP level was found to be high in sarcoidosis patients under steroid therapy (30). Dexamethasone and IL-4 were shown to increase SI-CLP mRNA expression from the macrophages.

It was reported that YKL-40 expression occurred both from macrophages and from the giant cells in the granuloma in an other study (31).

As a result, the increase in chitinase activity is believed to be related with the active macrophages and T cell mediated immunity in sarcoidosis. Chitinases can be used in defining the activity and monitoring the therapy.

#### CHITINASES and PULMONARY TUBERCULOSIS

Chitotriosidase level was found to be higher in pleural effusions due to tuberculosis than nonspecific pleural effusion. Besides, significant relation was demonstrated between chitotriosidase and adenosine deaminase activities (32). Blood serum YKL-40 level of patients with tuberculosis pleuritis was found to be higher than patients with effusions due to malign or cardiac causes (33).

#### CHITINASES and CYSTIC FIBROSIS

There are reported studies encouraging the usage of YKL-40 as a marker in cystic fibrosis. In a recent study, YKL-40 level has been found to be higher in blood and sputum specimens of the cystic fibrosis patients compared to control group (34).

#### CHITINASES and PNEUMONIA

YKL-40 level has been reported to be higher in patients' serum with pneumonia than patients with asthma, lung cancer and control group in a current study (33). YKL-40 level can be high especially in streptococcal pneumonia. YKL is secreted from the localised activated macrophages and neutrophils in the inflammation region.

#### CHITINASES and LUNG CANCER

Within the chitinases, although YKL-40's biological role is not clear, it is thought to take part in the proliferation, differentiation, angiogenesis and tissue remodeling of the malign cells (35).

YKL-40 is increased in the serum of patients with solid tumours. YKL-40 level is found to be higher in lung cancer patients (36). It is believed that the increase in YKL-40 level is a bad prognostic factor and related with short survival. YKL-40 mRNA expression was showed to be made strongly from the peritumoural macrophages (37).

#### CONCLUSIONS

Although the physiologic role of the chitinase is not yet exactly known, it has been shown that chitinases take place in the immune system and is a part of the natural

immune system in the clinical studies. Furthermore, chitinases can be used as a screening test in Gaucher disease and activity and follow up in sarcoidosis so new and comprehensive clinical studies are required. In this way the pathogenesis and different therapies of many diseases can be found by the help of these studies.

#### CONFLICT of INTEREST

None declared.

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