Role of breast regression protein-39/YKL-40 in asthma and allergic responses

Chun Geun Lee,* Jack A Elias

Section of Pulmonary and Critical Care Medicine, Yale University School of Medicine, New Haven, CT, USA

INTRODUCTION

BRP-39 and its human homolog YKL-40 have been regarded as a prototype of chitinase-like proteins (CLP) in mammals. Exaggerated levels of YKL-40 protein and/or mRNA have been noted in a number of diseases characterized by inflammation, tissue remodeling, and aberrant cell growth. Asthma is an inflammatory disease characterized by airway hyperresponsiveness and airway remodeling. Recently, the novel regulatory role of BRP-39/YKL-40 in the pathogenesis of asthma has been demonstrated both in human studies and allergic animal models. The levels of YKL-40 are increased in the circulation and lungs from asthmatics where they correlate with disease severity, and CHI3L1 polymorphisms correlate with serum YKL-40 levels, asthma and abnormal lung function. Animal studies using BRP-39 null mutant mice demonstrated that BRP-39 was required for optimal allergen sensitization and Th2 inflammation. These studies suggest the potential use of BRP-39 as a biomarker as well as a therapeutic target for asthma and other allergic diseases. Here, we present an overview of chitin/chitinase biology and summarize recent findings on the role of BRP-39 in the pathogenesis of asthma and allergic responses.

Key Words: BRP-39; human CHI3L1 protein; asthma; hypersensitivity
view briefly overviews the general biology of the chitin/chitinases and then focuses on the biological role of BRP-39/YKL-40 in the pathogenesis of asthma and allergic responses.

**BIOLOGY OF CHITIN, CHITINASES, AND CHITINASE-LIKE PROTEINS**

**Chitin and chitinases**

Chitin is a polymer of N-acetylglucosamine which has no mammalian counterpart. Following the cellulose in wood and paper, chitin is the second most abundant polysaccharide in nature. It is an essential component of fungal cell walls, the exoskeletons of crabs, shrimp and insects, the microfilarial sheath of nematodes and the digestive tracts of many insects. These pathogens use chitin in a number of ways in their life cycles. Most commonly, chitin protects the pathogen from the harsh conditions inside the animal or plant host or in its environment. Thus, an absence of chitin can lead to the death of the pathogen. Chitin deposition is regulated by biosynthesis and degradation. Chitinases, which are endo-b-1,4-N-acetylglucosaminidases, are key degrading enzymes that have been studied most intensely in lower life forms. They are produced in significant quantities by hosts defending against infections with chitin-containing organisms. This attempt to damage the chitin coat of the infecting organism is part of the innate immune response against a chitin-containing pathogen. It also produces differentially sized chitin fragments which can trigger innate immunity pattern recognition receptors to induce IL-17, TNF and/or IL-10 elaboration. Chitinases also contribute to the life cycle of chitin-containing fungi and parasites where they control growth and molting. They are also used by pathogens to invade or exploit chitin-containing structures in the host. This allows them to establish successful infections and thus play a critical role(s) in the transmission of infection from one vertebrate host to another by insect vectors. As a result of the importance of chitin in the protection of pathogens and the importance of appropriately regulated chitinase production in the life cycle of pathogens, chitin synthesis inhibitors and chitinase inhibitors have received significant attention as potential biopesticides to eradicate insects, fungi and helminthic parasites.

**Mammalian chitinase and chitinase–like genes**

Until recently it was assumed that mammals lacked chitinases. Recent studies in humans and rodents, however, have identified a family of chitinases and CLP in both species referred to as the 18 glycosyl hydrolase family. Acidic mammalian chitinase (AMCase), chitotriosidase, oviductin, YKL-40 and YKL-39 have been described in humans, while YM-1, YM-2, AMCase, oviductin, and BRP-39 have been described in mice. Recent studies from our laboratory have also described mouse chitotriosidase. YM-1 and YM-2 may be mouse-specific because comparable genes have yet to be described in man. They are produced by macrophages after parasitic or fungal infection. AMCase is produced by epithelial cells, macrophages and eosinophils at sites of Th2 inflammation. Interestingly, IL-13 is necessary and sufficient for the induction of this chitinase. In all cases, these moieties have a moderate degree of sequence homology with lower life form chitinases. However, in contrast to the chitinases in lower life forms, only chitotriosidase and AMCase have true chitin-degrading activity. Because of mutations in their highly conserved putative enzyme sites, BRP-39, YKL-40 and the other CLP do not have chitinase activity. As a result, their roles in biology are particularly enigmatic. A complete understanding of the biology of the chitinases and CLP requires elucidation of the roles of true chitinases and the chitinase-like proteins. Insights into the roles of AMCase have been obtained from studies in our laboratory and others. Recent studies using transgenic and null mutant mice shed light on the biologic properties of BRP-39 and YKL-40, the murine and human versions of this prototypic CLP in the development of allergic responses and tissue remodeling.

**Functions of mammalian chitinase–like proteins**

One of the most pressing issues in chitinase biology relates to our almost complete lack of understanding of the functions of these strongly conserved (and therefore presumably biologically important) moieties in mammals and man. Mammalian CLP are induced at sites of inflammation (such as parasitic infections) and remodeling. This raises the possibility that these molecules play active roles in human anti-parasite and anti-infective defense and repair responses. In accord with this concept, microarray analysis has demonstrated that the genes encoding chitinases are among the most prominently induced genes in parasite-challenged or IL-13-challenged lung tissue. It is important to point out, however, that the majority of the mammalian chitinase-like molecules do not have true chitinase activity (only chitotriosidase and AMCase have chitinolytic activity). Thus, the biologic roles of these molecules are even less adequately understood. It is reasonable to believe, however, that mammalian enzymes with true chitinase activity (such as AMCase and chitotriosidase) can play a direct role in host responses to chitin-containing pathogens. It is also reasonable to postulate that chitinase-like proteins such as BRP-39/YKL-40 can also play a role as sentinels that trigger responses to parasites, infections and/or antigen challenge; (b) attract eosinophils and T cells to sites of parasitic infection and/or; (c) generate or modulate tissue inflammation, immunity and/or remodeling. Recently, with the development of BRP-39 null mutant mice and lung specific YKL-40 overexpressing transgenic mice, in vivo regulatory role of BRP-39/YKL-40 in allergic inflammation and tissue response have been described. These studies demonstrated that BRP-39 is a key regulator of Th2 inflammation, M2 macrophage differentiation and Th2 cell and
macrophage apoptosis/cell death. These findings provide novel insights into the in vivo roles of BRP-39 in allergic sensitization process and effector function of Th2 cytokines. They represent a new level of understanding about the processes that regulate inflammatory cell survival and tissue remodeling responses, the pathologic hallmarks of asthma and allergic diseases.

Chitinase and chitinase-like proteins (C/CLP) in tissue remodeling

Recently, a number of studies suggest an important role of C/CLP in disease pathogenesis characterized by inflammation and pathologic tissue remodeling. The activity and levels of chitotriosidase in serum and BAL were higher in the patients with sarcoidosis, or with idiopathic pulmonary fibrosis, than in controls. Several studies also suggested that CLP such as YKL-40 or mouse Ym-1 or Ym-2 could be involved in tissue remodeling processes. Serum YKL-40 was significantly related to the degree of liver fibrosis, and staining of YKL-40 antigen was higher in areas with fibrosis, particularly in areas with active fibrogenesis. The animal models that accompany this tissue remodeling process also demonstrated significant changes in C/CLP expression at sites of inflammation or remodeling. Th2-inducing pathogens Schistosoma mansoni and Nippostrongylus brasiliensis cause granulomatous inflammation and liver fibrosis in the infected mice. In that model, AMCase and Ym-1 expression were significantly increased along with type 2 cytokines such as IL-13 and IL-4. In the mice with pulmonary fibrosis induced by crystalline silica exposure, or herpesvirus, there are close associations between expression of C/CLP and the degree of tissue remodeling. In this regard, it is intriguing to speculate that C/CLP, such as AMCase or YKL-40, play an important role in tissue remodeling process in chronic asthmatic patients. However, it is still not clear whether C/CLP actively participate in the tissue remodeling process or indirectly modulate the process through regulation of other cytokines and/or growth factors. Further mechanistic studies using specific gene targeted animal models or transgenic models will be required to define more specific functions of C/CLP in tissue remodeling processes.

REGULATORY ROLE OF BRP-39/YKL-40 IN ASTHMA AND ALLERGIC RESPONSES

Role of BRP-39 in allergic inflammation and tissue remodeling

Recently, BRP-39 null mutant mice and lung-specific YKL-40 overexpressing transgenic mice have been generated and used to define the functional role of BRP-39 in allergic and Th2 cytokine effector functions. These studies demonstrated that the null mutant mice have a significant defect in antigen-induced Th2 inflammation and IL-13-inuced inflammation and remodeling. These studies further demonstrated that BRP-39 and YKL-40 accomplish this, at least in part, by inhibiting inflammatory cell (T cell, macrophage and eosinophil) apoptosis/cell death while inhibiting Fas expression and stimulating protein kinase B/AKT phosphorylation. BRP-39 and YKL-40 were also shown to stimulate dendritic cell accumulation and activation, and to induce alternative macrophage activation. These studies suggest that BRP-39 may involve multiple stages of allergic responses by regulation of sensitization and Th2 cytokine effector functions. The defects in antigen sensitization and Th2 inflammation in BRP-39 null mutant mice can be explained by a marked decrease in the numbers of myeloid and plasmacytoid dendritic cells and the ability of these cells to be activated after antigen exposure. The hypothetical regulatory pathways of BRP-39 in allergic inflammation and tissue remodeling response has been illustrated in the Fig. 1. However, the exact regulatory mechanism of BRP-39 in dendritic cell function to drive Th2 polarization still remains to be determined. The specific role of BRP-39 in allergic response was further supported by the rescue experiment by generating BRP-39 null mice with epithelial cell-specific YKL-40 transgenic mice. In these mice, the epithelial YKL-40 totally rescues the deficient Th2 response in BRP-39 null animals, suggesting that secreted YKL-40 is an important soluble factor driving asthma-like Th2 inflammatory responses. These studies also identified a novel regulatory function of BRP-39 in IL-13-induced tissue fibrosis. Previous studies from our laboratory demonstrated that the fibrogenic effects of IL-13 are mediated, at least in part, by the ability of IL-13 to induce and activate TGF-β. Intriguingly, TGF-β induction of the lungs of IL-13 transgenic mice was significantly decreased in mice with a deficiency of BRP-39. It may explain the general regulatory role of BRP-39 in tissue remodeling in various diseases. However, the cellular and molecular mechanism of BRP-39 intervening IL-13-induced TGF-β production and activation need to be further determined. Finally, BRP-39 has a potential regulatory role in cell death responses that may responsible for proinflammatory roles of BRP-39 in allergic inflammation and in other inflammatory diseases, at least in part. BRP-39 has been shown to inhibit Fas- or TNF-α-induced cellular apoptosis while enhancing PKB/Akt pathways in macrophages and T cells. The properties of YKL-40 in activating MAP kinase and PKB/Akt pathways have been demonstrated in vitro assays with connective tissue cells. Inflammatory cell apoptosis has been regarded as a mechanism of resolution of inflammation. Thus, further mechanistic evaluation on the regulatory role of BRP-39 in specific apoptosis pathways will be necessary to understand the in vivo function of BRP-39 in asthmatic inflammation and tissue remodeling.

YKL-40 as a biomarker and potential therapeutic target

A variety of inflammatory cells (e.g., neutrophils, macrophages and differentiating monocytes) as well as structural cells (e.g., differentiated smooth muscle cell, chondrocytes, synovial cells, endothelial cells, and tumor cells) endogenously
express YKL-40. Intriguingly, increased levels of YKL-40 protein and/or mRNA have been noted in a variety of diseases characterized by inflammation, tissue remodeling, and aberrant cell growth. They include rheumatoid arthritis, osteoarthritis, giant cell arthritis, sarcoidosis, sclerosis, diabetes, atherosclerosis, inflammatory bowel disease, liver fibrosis, and several malignancies. Recently, elevated levels of YKL-40 in the BAL and serum in smokers with COPD were reported. These significant associations of YKL-40 with a variety of disease development or progression renders YKL-40 as a useful diagnostic or prognostic biomarker. In addition, in many of these disorders the levels of YKL-40 reflect the activity and natural history of the disease. This is nicely illustrated in studies from our laboratory and others which demonstrated that elevated levels of serum YKL-40 are seen in patients with asthma which correlate with the levels of lung tissue YKL-40 and disease severity. These studies also highlighted polymorphisms in chitinase 3-like-1 that correlated with the levels of circulating YKL-40, the presence of asthma, and compromised lung function. The potential importance of YKL-40 can also be seen in rheumatoid arthritis, coronary artery disease, solid cancers and death in the elderly where elevated serum YKL-40 levels correlate with the severity of joint involvement, the number of blocked coronary arteries, short disease free intervals, and all cause mortality, respectively. As a result, YKL-40 is a prognostic biomarker and has been proposed to be a therapeutic target in conditions characterized by acute or chronic inflammation, extracellular matrix remodeling, fibrosis and cancer. In this regard, recent animal studies demonstrating an essential role of BRP-39 in the pathogenesis of allergic inflammation and tissue remodeling, legitimate the usefulness of BRP-39/YKL-40 as a therapeutic target for asthma and other allergic diseases.

**UN SOLVED ISSUES AND FUTURE RESEARCH NEEDS**

**Mechanisms underlying BRP-39/YKL-40 effector responses**

BRP-39/YKL-40 is a secreted protein that is synthesized with a propeptide that is removed to reveal the mature protein. X-ray crystal analysis has revealed a (beta/alpha) 8 barrel fold with a 43 AA carbohydrate binding cleft. Despite this structural knowledge, the carbohydrate binding repertoire of BRP-39/YKL-40 has not been fully defined. Its ability to bind with high affinity to chitin has been noted above. Recently, it has been shown to bind to heparin and collagen with lower affinity. The roles of BRP-39/YKL-40 in inflammation, remodeling and angiogenesis and its ability to act as a mitogen, chemotactic factor and growth factor are believed to be the result of cell surface li-
In accord with this concept, BRP-39/YKL-40 has been shown to activate mitogen activated protein kinase (MAPK), PI-3 kinase (PI3K) and PKB/Akt signaling pathways. While the activation of these pathways is linked to ligand binding to a cell surface receptor, no cell surface BRP-39/YKL-40 binding proteins have been identified. In fact, a biologically active receptor for any C/CLP has not been identified. Thus, the identification of the ligand-receptor interactions that mediate the effector responses of BRP-39/YKL-40 and related moieties is one of the most pressing challenges in C/CLP biology.

**BRP-39 in allergic sensitization and allergic responses with chitin or chitin-containing allergen**

Although it has been shown that BRP-39 is required for optimal sensitization with ovalbumin (non-chitin containing allergen), the exact role of BRP-39 in sensitization processes is still largely undefined. How does BRP-39/YKL-40 regulate dendritic cell functions or subsequent T cell polarization? What is the role of BRP-39/YKL-40 in allergic responses with chitin or chitin-containing allergens (e.g., house dust mite, pollen, Ragweed etc.) other than ovalbumin? Although some evidence suggests that BRP-39 plays a similar role with chitin-containing house dust mite challenge as with ovalbumin, the regulatory role of BRP-39 in allergic responses with chitin or chitin-containing allergen has not been fully evaluated. Those are the remaining questions that need to be fully addressed in the future for a clearer understanding on the role of BRP-39/YKL-40 in asthma and other allergic responses.

**Potential interaction of BRP-39 with AMCase or other C/CLP**

Previous studies demonstrated that AMCase also play an important role in allergen-induced Th2 inflammation and effector function of IL-13. Because these functional similarities, it raises the question regarding a potential redundancy of C/CLP in the regulation of allergic inflammation. Although there is overlap in the expression and regulatory pathways between these two molecules, many pieces of evidence suggest specific regulatory roles of BRP-39 that are distinctive from those of AMCase. First, the regulation of the expression of BRP-39 and AMCase is not the same: IL-13 induces both AMCase and BRP-39, but BRP-39 was induced by IFN- while AMCase was not. Second, double immunohistochemistry demonstrated that sites of BRP-39 and AMCase differentially expressed, depending on the cells. BRP-39 staining was more pronounced in alveolar epithelial cells and macrophages, while AMCase had its abundance in airway epithelial cells. Lastly, the levels of AMCase were not significantly changed in IL-13 transgenic lungs with BRP-39 null mutation. Because IL-13-induced inflammatory and tissue phenotypes were drastically changed in the absence of BRP-39, we can speculate that BRP-39 is required for IL-13 effector functions independent of AMCase. However, we still do not have clear answers regarding whether these two molecules have close interaction in the regulation of allergic responses, partly because currently we do not have appropriate murine models such as AMCase null mutant mice or transgenic mice to evaluate specific function of AMCase in relation to BRP-39. In this regard, comprehensive in vivo and in vitro studies to define potential C/CLP interactions will be necessary to understand C/CLP regulation of allergic responses.

**CONCLUSIONS**

YKL-40, a human homolog of BRP-39, a chitinase-like protein, has been reported to be associated with a number of diseases characterized by inflammatory and tissue remodeling responses. However, the in vivo role of BRP-39/YKL-40 in the pathogenesis of specific diseases has been elusive until the recent development of gene-specific null mutant mice and overexpressing transgenic mice. Studies from our laboratory demonstrate that BRP-39 is stimulated by IL-13 and Th2 inflammation and that null mutations of BRP-39 diminish Th2 and IL-13-induced inflammation and remodeling. They also demonstrate that BRP-39/YKL-40 inhibits T cell and macrophage apoptosis/cell death while inhibiting Fas expression, increasing the activation of PKB/Akt and inducing M2 macrophage differentiation. When combined with the recent demonstration that the levels of YKL-40 are increased in the circulation and lungs from asthmatics where they correlate with disease severity and that CHI3L1 polymorphisms correlate with serum YKL-40 levels, asthma and abnormal lung function, these studies further provide novel insight on the regulatory roles of BRP-39 in IL-13 and/or Th2-mediated inflammation and tissue responses. They also legitimize the usefulness of BRP-39/YKL-40 as a diagnostic biomarker as well as potential therapeutic target of asthma and other allergic inflammatory diseases. For better understanding of the effector function of BRP-39/YKL-40 in inflammation and tissue remodeling, more mechanistic studies directed to define the molecules that interact with these chitinase-like proteins such as receptor or signaling proteins, will be warranted in the future.

**ACKNOWLEDGMENTS**

This work was partly supported by the Grants from National Institute of Health, RO1-HL-084225 and RO1-HL-081639. We thank Susan Ardito for her excellent secretarial assistance.

**REFERENCES**

1. Morrison BW, Leder P. neu and ras initiate murine mammary tumors that share genetic markers generally absent in c-myc and int-2-initiated tumors. Oncogene 1994;9:3417-26.
2. Reijman JJ, Hurley WL. Isolation and characterization of a novel 39 kDa whey protein from bovine mammary secretions collected dur-
Role of breast regression protein-39/YKL-40 in asthma and allergic responses

17. Sohn MH, Lee JH, Kim KW, Kim SW, Lee SH, Kim KE, Kim KH, Lee CG, Elias JA, Lee MG. Genetic variation in the promoter region of chitinase 3-like 1 is associated with atopy. Am J Respir Crit Care Med 2009;179:449-56.

18. Lee CG, Harl D, Lee GR, Koller B, Matsuura H, Da Silva CA, Sohn MH, Cohn L, Homer RJ, Kozhich AA, Humble A, Kearley J, Coyle AJ, Chupp G, Reed J, Flavell RA, Elias JA. Role of breast regression protein 39 (BRP-39)/chitinase 3-like-1 in Th2 and IL-13-induced tissue responses and apoptosis. J Exp Med 2009;206:1149-66.

19. Shibata Y, Foster LA, Bradfield JE; Myrvik QN. Oral administration of chitin down-regulates serum IgE levels and lung eosinophilia in the allergic mouse. J Immunol 2000;164:1314-21.

20. Boot RG, Blommaart EF; Swart E, Ghausharali-van der Vlugt K, Bijl N, Moe C, Place A, Aerts JM. Identification of a novel acidic mammalian chitinase distinct from chitotriosidase. J Biol Chem 2001;276:6770-8.

21. Boot RG, Renkema GH, Verhoeck, Strijland A, Biek J, de Meulemeester TM, Mannens MM, Aerts JM. The human chitotriosidase gene. Nature of inherited enzyme deficiency. J Biol Chem 1998;273:25680-5.

22. Araujo AC, Souto-Padron T, de Souza W. Cytochemical localization of carbohydrate residues in microfilariae of Wuchereria bancrofti and Brugia malayi. J Histochem Cytochem 1993;41:571-8.

23. Debono M, Gordee RS. Antibiotics that inhibit fungal cell wall development. Annu Rev Microbiol 1994;48:471-97.

24. Fuhrman JA, Piessens F; Wetherby J, Debackere B, Pieters T, Baert M. Chitin synthases in mammals. Amino acids 2004;23:223.

25. Shahabuddin M, Kaslow DC. Plasmodium: parasite chitinase and its role in malaria transmission. Exp Parasitol 1994;79:85-8.

26. Shahabuddin M, Vinetz JM. Chitinases of human parasites and their implications as antiparasitic targets. In: Jolles P; Muzzarelli RAAR, editors. Chitinases and Chitinases. Basel: Birkhauser Verlag; 1999. p. 223.

27. Da Silva CA, Harl D, Liu W, Lee CG, Elias JA. TLR-2 and IL-17A in chitin-induced macrophage activation and acute inflammation. J Immunol 2008;181:4279-86.

28. Da Silva CA, Chalouni C, Williams A, Hart D, Lee CG, Elias JA. Chitin is a size-dependent regulator of macrophage TNF and IL-10 production. J Immunol 2009;182:3573-82.

29. Shahabuddin M, Toyoshima T, Aiakawa M, Kaslow DC. Transmission-blocking activity of a chitinase inhibitor and activation of malarial parasite chitinase by mosquito protease. Proc Natl Acad Sci U S A 1993;90:4266-70.

30. Herrera-Estrella A, Chet I. Chitinases in biological control. Exs 1999;87:171-84.

31. Pali SR, Retnakaran A. Molecular and biochemical aspects of chitin synthesis inhibition. Exs 1999;87:85-98.

32. Bleau G, Massicotte F; Merlen Y, Boisvert C. Mammalian chitinase-like proteins. Exs 1999;87:221-27.

33. Chang NC, Hung SL, Hwa KY, Kato I, Chen JE, Liu CH, Chang AC. A macrophage protein, Ym1, transiently expressed during inflammation is a novel mammalian lectin. J Biol Chem 2001;276:17497-506.

34. Ward JM, Yoon M, Anver MR, Haines DC, Kudo G, Gonzalez FJ, Kimura S. Hyalinosis and Ym1/Ym2 gene expression in the stromal and respiratory tract of 129S1/SvJae and wild-type and CY-A1A deficient mice. Am J Pathol 2001;158:323-32.

35. Zheng T, Rabach M, Chen NY, Rabach L, Hu X, Elias JA, Zhu Z. Molecular cloning and functional characterization of mouse chitotriosidase. Gene 2005;357:37-46.
37. Guo L, Johnson RS, Schuh JC. Biochemical characterization of endogenously formed eosinophilic crystals in the lungs of mice. J Biol Chem 2000;275:8032-7.
38. Zhu Z, Zheng T, Homer RJ, Kim YK, Chen NY, Cohn L, Hamid Q, Elias JA. Acidic mammalian chitinase in asthmatic Th2 inflammation and IL-13 pathway activation. Science 2004;304:1678-82.
39. Reese TA, Liang HE, Tager AM, Luster AD, Van Rooijen N, Voehringer D, Locksley RM. Chitin induces accumulation in tissue of innate immune cells associated with allergy. Nature 2007;447:92-6.
40. Zou J, Young S, Zhu F, Gheyas F, Speak S, Wan Y, Wang L, Ding W, Billah M, McAllanathan T, Coffman RL, Egan R, Umland S. Microarray profile of differentially expressed genes in a monkey model of allergic asthma. Genome Biol 2002;3:research0020.
41. Zimmermann N, Mishra A, King NE, Fulkerseon PC, Doepker MP, Nikolaidis NM, Kindinger LE, Moulton EA, Aronow BJ, Rothenberg ME. Transcript signatures in experimental asthma: identification of STAT6-dependent and -independent pathways. J Immunol 2004;172:1815-24.
42. Ovhashi M, Arita H, Hayai N. Identification of a novel eosinophil chemotactic cytokine (EFC-L) as a chitinase family protein. J Biol Chem 2000;275:1279-86.
43. Bargagli E, Margolliaci M, Luddi A, Nikiforakis N, Perani MG, Grocco S, Perrone A, Rottoli P. Chitotriosidase activity in patients with interstitial lung diseases. Respir Med 2007;101:2176-81.
44. Bargagli E, Margolliaci M, Nikiforakis N, Luddi A, Perrone A, Grocco S, Rottoli P. Chitotriosidase activity in the serum of patients with sarcoidosis and pulmonary tuberculosis. Respiration 2007;75:548-52.
45. Johansen JS, Christoffersen P, Møller S, Price PA, Henriksen JH, Garbarsch C, Benfield TL, Ostergaard M, Ostergaard K, Lowgren-Nielsen P, Sonne-Holm S, Lorenzen I. Studies on YKL-40 in knee joints of patients with rheumatoid arthritis and osteoarthritis. Inflamm Res 2002;51:1233-43.
46. Volck B, Johansen JS, Stoltenberg M, Garbarsch C, Price PA, Ostergaard M, Ostergaard K, Lowgren-Nielsen P, Sonne-Holm S, Lorenzen I. Increased serum YKL-40 in patients with pulmonary sarcoidosis - a potential marker of disease activity? Respir Med 2005;99:396-402.
47. Nordenbaek C, Johansen JS, Halberg P, Wiik A, Garbarsch C, Ulman S, Price PA, Jacobsen S. High serum levels of YKL-40 in patients with systemic sclerosis are associated with pulmonary involvement. Acta Clin Scand 2005;214:427-34.
48. Lee CG, Homer RJ, Zhu Z, Lanone S, Wang X, Kotelnjakv S, Shiple J, Gotwals P, Noble PB, Chen Q, Senior RM, Elias JA. Interleukin-13 induces tissue fibrosis by selectively stimulating and activating transforming growth factor beta1. J Exp Med 2001;194:809-21.
49. Kolaczkowska E, Kozioł A, Płytczyk B, Arnold B. Inflammatory macrophages, and not only neutrophils, die by apoptosis during acute peritonitis. Immunobiology 2009. [Epub ahead of print]
50. Collison A, Foster PS, Mattes J. Emerging role of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) as a key regulator of inflammatory responses. Clin Exp Pharmacol Physiol 2009;36:1049-53.
51. Volck B, Price PA, Johansen JS, Sørensen O, Benfield TL, Nielsen HJ, Calafat J, Borregaard N. YKL-40, a mammalian member of the chitinase family, is a matrix protein of specific granules in human neu-trophils. Proc Assoc Am Physicians 1998;110:351-60.
52. Johansen JS, Olie T, Price PA, Hashimoto S, Ochs RL, Lotz M. Regulation of YKL-40 production by human articular chondrocytes. Arthritis Rheum 2001;44:826-37.
53. Shackelton LM, Mann DM, Mills AJ. Identification of a 38-kDa heparin-binding glycoprotein (gp38k) in differentiating vascular smooth muscle cells as a member of a group of proteins associated with tissue remodeling. J Biol Chem 1995;270:13076-83.
54. Nishikawa KC, Mills AJ. gp38K (CHI3L1) is a novel adhesion and migration factor for vascular cells. Exp Cell Res 2003;287:79-87.
55. Krause SW, Rehli M, Kreutz M, Schwarzfischer L, Paulauskis JD, Andreessen R. Differential screening identifies genetic markers of monocyte to macrophage maturation. J Leukoc Biol 1996;60:540-5.
56. Junker N, Johansen JS, Andersen CB, Kristjansen PE. Expression of YKL-40 by peritumoral macrophages in human small cell lung cancer. Lung Cancer 2005;48:223-31.
57. Baeten D, Boots AM, Stenbakkens PG, Elevaert D, Boens E, Verheijden GE, Berheijden AM, Rijnders AW, Veys EM, de Keyser F. Human cartilage gp-39+, CD16+ monocytes in peripheral blood and synovium: correlation with joint destruction in rheumatoid arthritis. Arthritis Rheum 2000;43:1233-43.
58. Volck B, Johansen JS, Stoltenberg M, Garbarsch C, Price PA, Ostergaard M, Ostergaard K, Lowgren-Nielsen P, Sonne-Holm S, Lorenzen I. YKL-40 in giant cells and macrophages from patients with giant cell arteritis. Arthritis Rheum 1999;42:2624-30.
59. Johansen JS, Milman N, Hansen M, Garbarsch C, Price PA, Graudal N. Increased serum YKL-40 in patients with pulmonary sarcoidosis - a potential marker of disease activity? Respir Med 2005;99:396-402.
60. Lee CG, Homer RJ, Zhu Z, Lanone S, Wang X, Kotelnjakv S, Shiple J, Gotwals P, Noble PB, Chen Q, Senior RM, Elias JA. Interleukin-13 induces tissue fibrosis by selectively stimulating and activating transforming growth factor beta1. J Exp Med 2001;194:809-21.
70. Shostak K, Labunsky V, Dmitrenko V, Malisheva T, Shamayev M, Rozumenko V, Zozulya Y, Zehetner G, Kavsan V. HC gp-39 gene is upregulated in glioblastomas. Cancer Lett 2003;198:203-10.
71. Letuve S, Kozhich A, Arouche N, Grandaize M, Reed J, Dombret MC, Kiener PA, Aubier M, Coyle AJ, Pretolani M. YKL-40 is elevated in patients with chronic obstructive pulmonary disease and activates alveolar macrophages. J Immunol 2008;181:5167-73.
72. Wang Y, RIPA RS, Johansen JS, Gabrielsen A, Steinbruchel DA, Friis T, Bindslev L, Haack-Sorensen M, Jorgensen E, Kastrup J. YKL-40 a new biomarker in patients with acute coronary syndrome or stable coronary artery disease. Scand Cardiovasc J 2008;42:295-302.
73. Johansen JS, Jensen BV, Roslind A, Nielsen D, Price PA. Serum YKL-40, a new prognostic biomarker in cancer patients? Cancer Epidemiol Biomarkers Prev 2006;15:194-202.
74. Knudsen LS, Ostergaard M, Balslund B, Nørvestad E, Petersen J, Nielsen HI, Ejbjerg BJ, Szkudlarek M, Johansen JS. Plasma IL-6, plasma VEGF and serum YKL-40: relationship with disease activity and radiographic progression in rheumatoid arthritis patients treated with infliximab and methotrexate. Scand J Rheumatol 2006;35:489-91.
75. Rathcke CN, Vestergaard H. YKL-40, a new inflammatory marker with relation to insulin resistance and with a role in endothelial dysfunction and atherosclerosis. Inflamm Res 2006;55:221-7.
76. Johansen JS. Studies on serum YKL-40 as a biomarker in diseases with inflammation, tissue remodelling, fibroses and cancer. Dan Med Bull 2006;53:172-209.
77. Johansen JS, Pedersen AN, Schroll M, Jorgensen T, Pedersen BK, Bruunsgaard H. High serum YKL-40 level in a cohort of octogenarians is associated with increased risk of all-cause mortality. Clin Exp Immunol 2008;151:260-6.
78. Johansen JS, Jensen BV, Roslind A, Price PA. Is YKL-40 a new therapeutic target in cancer? Expert Opin Ther Targets 2007;11:219-34.
79. Coffman FD. Chitinase 3-Like-1 (CHI3L1): a putative disease marker at the interface of proteomics and glycomics. Crit Rev Clin Lab Sci 2008;45:531-62.