Potential role of chitinase 3-like-1 in inflammation-associated carcinogenic changes of epithelial cells

Katrin Eurich, Mayuko Segawa, Satoko Toei-Shimizu, Emiko Mizoguchi

Abstract
The family of mammalian chitinases includes members both with and without glycohydrolase enzymatic activity against chitin, a polymer of N-acetylglucosamine. Chitin is the structural component of fungi, crustaceans, insects and parasitic nematodes, but is completely absent in mammals. Exposure to antigens containing chitin- or chitin-like structures sometimes induces strong T helper type-I responses in mammals, which may be associated with the induction of mammalian chitinases. Chitinase 3-like-1 (CHI3L1), a member of the mammalian chitinase family, is induced specifically during the course of inflammation in such disorders as inflammatory bowel disease, hepatitis and asthma. In addition, CHI3L1 is expressed and secreted by several types of solid tumors including glioblastoma, colon cancer, breast cancer and malignant melanoma. Although the exact function of CHI3L1 in inflammation and cancer is still largely unknown, CHI3L1 plays a pivotal role in exacerbating the inflammatory processes and in promoting angiogenesis and remodeling of the extracellular matrix. CHI3L1 may be highly involved in the chronic engagement of inflammation which potentiates development of epithelial tumorigenesis presumably by activating the mitogen-activated protein kinase and the protein kinase B signaling pathways. Anti-CHI3L1 antibodies or pan-chitinase inhibitors may have the potential to suppress CHI3L1-mediated chronic inflammation and the subsequent carcinogenic change in epithelial cells.

INTRODUCTION
Chitin, the linear polymer of β-1,4-linked N-acetylglucosamine (GlcNAc), is a structural component of the cell walls and coatings of many organisms, and represents the second most abundant polysaccharide in nature after cellulose. Chitin efficiently protects crustaceans, insects, parasites, fungi, and other pathogens from the harsh adverse effects of their environments and/or hosts[1]. Although chitin has not been found in mammals, several mammalian proteins with homology to fungal, bacterial, or plant chitinases have been identified[2-6]. Chitotriosidase (CHIT1), and acidic mammalian chitinase (AMCase) are the only 2 of these proteins demonstrating chitinolytic (glycohydrolase) activity, while none of the other mammalian chitinases show enzymatic activity despite the retention and conservation of the substrate-binding cleft of the chitinases[7-9]. Therefore, the latter chitinases are called chitinase-like-lectins (Chi-lectins). Only recently, our group and others have identified the important biological roles of mammalian chitinases in chronic inflammatory conditions including inflammatory bowel disease (IBD), type 2 diabetes, proliferative dermatitis and allergic bronchial asthma[10-16]. One mammalian chitinase, chitinase
3-like-1 (CHI3L1, also known as YKL-40 or HC-gp39) is overexpressed in many pathological conditions including fibroblastic change in liver cirrhosis, increased deposition of connective tissue components and hyperplastic synovium in rheumatoid arthritis, and increased cellular infiltration as well as epithelial proliferation in chronic colitis. CHI3L1 is difficult to detect in the body of normal individuals and the biological role of CHI3L1 in embryonic development or distribution of this molecule in normal tissues is still largely unclear. Interestingly, significantly high amounts of CHI3L1 are detected in the involuting mammary gland upon cessation of lactation[15], however the exact biological role of CHI3L1 in this process has not yet been elucidated. CHI3L1 can also directly regulate the critical processes of adhesion and migration in vascular smooth muscle cells in vitro[15]. In addition many groups have reported that CHI3L1 is expressed on many different types of human solid cancers[3,10,18,19]. Surprisingly, CHI3L1 seems to be a useful “prognosticator”, or indicator of prognosis, and may also be a potential “tumor marker” in screening and monitoring of cancer patients[20-23]. In this review article, we will discuss the potentially important biological functions of mammalian chitinases, in particular CHI3L1, during the development of chronic inflammatory and the subsequent inflammation-mediated oncogenic processes in epithelial cells.

INFLAMMATORY DISORDERS MEDIATED BY MAMMALIAN CHITINASES

Chitin, a polymer of GlcNAc, is produced copiously by a wide variety of organisms such as crustaceans (e.g. shrimp and crab), insects, fungi, amphibians, parasitic nematodes, and other marine organisms[24,25]. However, chitin is completely absent in mammals including humans and mice[26]. Therefore, it was believed for a long time that mammals were not capable of producing chitinolytic endoglucosaminases in the body, but Hollak et al[27] first discovered CHIT1, a functional and structural homolog to the chitinases of other species, in serum samples of Gaucher disease patients. Gaucher disease is a genetic disorder causing a lack of the lysosomal enzyme glucocerebrosidase and is characterized by accumulation of macrophage-like Gaucher cells which have glycosphingolipids in cytosolic compartments[28]. The serum level of CHIT1 is upregulated approximately 1000-fold in patients with Gaucher disease as compared to normal individuals and the enzyme shows glycohydrolase activity against chitin and other chitin-like substances (e.g. β-nitrophenyl chito-oligosaccharides)[29]. Subsequent studies revealed that the increased CHIT1 activity in Gaucher disease patients is associated with aberrant macrophage activation[29], and the activity can be used as a marker of disease severity and therapeutic response in Gaucher disease[30]. Boot et al[31] reported that approximately 6% of various ethnic groups have a homozygous mutant allele of 24 bp duplication of the CHIT1 gene, resulting in a complete lack of CHIT1 enzymatic activity. Increased rates of nematode infection seemed to be associated with the mutation[32]. The CHIT1 cDNA was cloned by Boot et al[33] revealing that this molecule has a strong sequential homology to other chitinases belonging to the family 18 of glycosyl hydrolases. CHIT1 contains a complete chitin-binding domain in the C-terminus region that connects with the catalytic groove by a hinge region[34]. The chitin-binding domain of CHIT1 efficiently binds with chitin polymers as shown by structural analysis[35]. Under inflammatory conditions, CHIT1 expression of pathogenic macrophages is significantly upregulated in the inflamed tissues[36]. In addition to CHIT1, there is another mammalian chitinase, AMCase, which shows high structural homology with CHIT1, has an optimal enzymatic activity at around pH2 and exhibits glycohydrolase enzymatic activity. Full-length cDNA of mouse and human AMCase was first cloned in 2001[37], but an exciting biological role of AMCase was revealed by Zhu et al[38] only recently: the group noticed a formation of crystals in lung tissues of mice with an asthma-like disease model and identified that the crystals were mammalian chitinase[39]. The production of AMCase was significantly upregulated in the epithelial cells and tissue macrophages of patients with asthma, but the expression at messenger RNA level was undetectable from patients without lung disease[40,41]. Interestingly, anti-AMCase specific antibody as well as pan-chitinase inhibitor allosamidin efficiently ameliorate airway hyperresponsiveness and inflammatory cell infiltrations in the lung of aeroallergen-challenged mice[42], suggesting that AMCase would be an attractive therapeutic target in allergic asthma. A common genetic variant within exon 4 of AMCase from A to G at position 47 (termed A47G) and another variant K17R showed significant association with pediatric asthma. These genetic results support strongly that AMCase is associated with the development of asthma. Recently, Elias’s group found that not only AMCase but also CHI3L1 levels in serum as well as lung tissue were significantly elevated in 3 cohorts of patient (at Yale University, University of Paris, and University of Wisconsin) with asthma[43]. Expression levels of CHI3L1 in the serum and lungs closely correlated with the severity of asthma, suggesting that the CHI3L1 molecule plays both a primary and a secondary role in asthma patients[44]. In addition, another group also identified that a promoter single nucleotide polymorphism (C131G) in CHI3L1 was strongly associated with elevated serum levels of CHI3L1, pulmonary function, asthma, and bronchial hyperresponsiveness[45]. From those results, it appears mammalian chitinases are somehow associated with the development of inflammatory conditions in mucosal tissues. The association between the mammalian chitinases and inflammatory disorders is summarized in Table 1.
Table 1 Mammalian chitinases in inflammatory disorders

| Location | Disorders | Chitinase type | Ref. |
|----------|-----------|---------------|------|
| Airway   | Bacteremia with S. pneumoniae | CHI3L1 | [42,43] |
|          | Bronchial asthma | CHI3L1, AMCase, YM1 | [43,44] |
|          | COPD | CHI3L1 | [45] |
|          | Cystic fibrosis | AMCase, CHIT1 | [46] |
|          | Rhinosinusitis | AMCase | [47] |
|          | Sarcoidosis | CHIT1 | [48] |
| Blood    | Bacterial septicaemia | CHI3L1 | [49] |
| Brain    | Encephalitis | CHI3L1 | [50,51] |
|         | Meningitis | CHI3L1 | [52] |
| Disc/Joint | Intervertebral disc degeneration | CHI3L1 | [53] |
|          | Juvenile idiopathic arthritis | CHIT1 | [54] |
|          | Osteoarthritis, RA | CHI3L1 | [55,56] |
| Eye      | Conjunctivitis | AMCase | [57,58] |
| GI tract | Helicobacter gastritis | CHI3L1, CHIT1 | [59,60] |
|          | Inflammatory bowel disease | CHI3L1 | [61] |
| Heart    | Acute myocardial infarction | CHI3L3, CHI3L1 | [62,63] |
|          | Coronary artery disease | CHIT1 | [64] |
| Liver    | Chronic hepatitis C, LC | CHI3L1 | [65,66] |
|          | Fatty liver disease | CHIT1 | [67,68] |
|          | Hepatic fibrosis | CHI3L1 | [69] |
| Oral cavity | Periodontitis | Chitinase | [70,71] |
| Systemic | Gaucher disease | CHIT1 | [72] |
|          | Systemic sclerosis | CHI3L1 | [73,74] |

COPD: Chronic obstructive pulmonary disease; LC: Liver cirrhosis; RA: Rheumatoid arthritis; CHI3L1: Chitinase 3-like-1; AMCase: Acidic mammalian chitinase; CHIT1: Chitotriosidase; YM1: Chitinase-like lectin.

ROLE OF CHI3L1 IN THE PATHOGENESIS OF CHRONIC INFLAMMATION

Although CHI3L1 was first identified in 1993,[3] its biological function has been largely undetermined. CHI3L1 possesses a functional carbohydrate-binding motif which allows binding with a polymer or oligomer of GlcNAc, but CHI3L1 lacks enzymatic activity entirely. The lack of enzymatic activity in CHI3L1 can be explained by the substitution of leucine for an essential glutamic acid residue within the active site of CHI3L1.[30] Therefore, chitinases without enzymatic activity (including CHI3L1) act as chi-lectin[40] because of the presence of a preserved carbohydrate-binding motif. Recently, Recklies et al.[46] reported that CHI3L1 promotes the growth of human synovial cells and fibroblasts, raising the possibility that this protein plays a role in the pathological conditions leading to arthritis and tissue fibrosis. Of note, increased circulating levels of CHI3L1 have been reported in the serum of patients with several inflammatory conditions including IBD [Crohn’s disease (CD) and ulcerative colitis (UC)],[47,48] asthma,[49,50] and liver cirrhosis[51]. Serum CHI3L1 is rarely detectable in healthy individuals[48], and therefore CHI3L1 has recently been proposed as a useful marker for indicating inflammatory activity and poor clinical prognosis for IBD.[49]. A soluble form of CHI3L1 seems to be secreted by a wide variety of mammalian cells in vitro, including activated neutrophils, granulocytes, differentiated macrophages and colonic epithelial cells (CECs).[52] CHI3L1 is strongly expressed by macrophages in the synovial membrane of patients with rheumatoid arthritis (RA) and a polarized IFN- mediated proinflammatory Th1-type immune response has been observed in half the patients with RA. In contrast, peripheral mononuclear cells from healthy individuals strongly react against the CHI3L1 antigen and eventually produce a regulatory cytokine IL-10.[44] These results strongly suggest that CHI3L1-mediated immune responses in RA patients are somehow shifted from an IL-10 dominated immunoregulatory response to an IFNγ-dominated proinflammatory phenotype.[44] In addition, serum levels of CHI3L1 are positively correlated with the severity of arthritis.[40] Interestingly, peripheral blood T cells from RA patients proliferate in response to RA-associated DR4 (DRB1*0401) peptide which contains a potential self-reactive motif preserved within human CHI3L1.[40] In fact, the specific motif within CHI3L1 is responsible for the development and relapse of joint inflammation seen in Balb/c mice, suggesting that CHI3L1 is able to serve as an auto-antigen for arthritis in mice as well as humans.[40]. Intranasal as well as oral auto-antigen administration is one of the most effective strategies for inducing immuno-tolerance.[47,48]. Indeed, several groups have tried to administer CHI3L1 intranasally in animal models of arthritis,[49,50] as well as RA patients with moderate disease activity,[51] and the protein administration effectively suppresses the disease activity by downregulating the Th1-type immune response without showing any adverse effects. Therefore, CHI3L1 seems to be the cross-tolerance inducing protein in chronic arthritis which effectively downregulates the pathogenic immune responses. It is possible that nasal administration of CHI3L1 represents an attractive approach for suppressing the clinical manifestation of chronic types of inflammation as well as autoimmune diseases.

Our group recently identified that CHI3L1 plays a unique role during the development of intestinal inflammation: the molecule is induced in both colonic lamina propria macrophages and CECs during the course of intestinal inflammation in experimental colitis models as well as in patients with IBD.[40]. Gentamicin protection assays using intracellular bacteria, including Salmonella typhimurium and adherent invasive Escherichia coli show that CHI3L1 is required for the enhancement of adhesion and invasion of these bacteria on/into CECs and acts as a pathogenic mediator in acute colitis. It has been suggested that a genetic defect against intracellular bacterial infection is strongly associated with the development of CD, and an increased prevalence of intracellular bacteria in the ileal biopsies and surgical specimens of CD patients has been reported previously.[42,43]. We also identified that the CHI3L1 molecule particularly enhances the adhesion of chitin-binding protein-expressing bacteria to CECs through the conserved amino-acid residues.[44]. Therefore, overexpression of CHI3L1 may be strongly associated with the intracellular bacterial adhesion and invasion on/into CECs in CD patients, who presumably have mutations in the susceptibility genes of CD including NOD2 (CARD 15), IL-23R, ATG16L1 and XBP-1.[45]. In contrast, in an aseptic condition such as bronchial asthma, epithelium-expressing CHI3L1 seems to play a regulatory role by rescuing Th2-type immune responses.[46]. Further
study will be required to fully prove the exact role of epithelium-expressing CHI3L1 in inflammatory conditions.

**EXPRESSION OF CHI3L1 IN VARIOUS SOLID TUMORS**

The biological function of CHI3L1 is still unclear, but it has been strongly hypothesized that CHI3L1 plays a pivotal role as a growth stimulating factor for solid tumors or has a suppressive/protective effect in the apoptotic processes of cancer cells[18] and inflammatory cells[56]. Based on an amino acid database search at the National Center for Biotechnology Information, CHI3L1 is expressed in a wide variety of human solid tumors as summarized in Table 2. In addition, elevated levels of CHI3L1 in serum and/or plasma have been detected in patients with different types of solid tumors (Table 2). Therefore, it is reasonable to predict that the serum level of CHI3L1 can be a reliable marker of progression of certain kinds of tumors and of a “bad prognosis” in patients with certain types of malignant tumors[18].

Many clinical laboratories have reported that CHI3L1 could be used as a novel tumor marker for ovarian cancer[55,56], small cell lung cancer[20], metastatic breast cancer[21], and metastatic prostate cancer[22,23]. In addition, several groups have reported that CHI3L1 is one of the most significant prognosis markers for cervical adenocarcinoma[58], recurrent breast cancer[59] and metastatic breast cancer[21], as well as advanced stages of breast cancer[59]. Interestingly, the CHI3L1 serum level could be a useful and sensitive biomarker for recurrence in locally advanced breast carcinoma[21] and metastatic breast cancer[21], as well as advanced stages of breast cancer[59]. Interestingly, the CHI3L1 serum level could be a useful and sensitive biomarker for recurrence in locally advanced breast carcinoma[21] and metastatic breast cancer[21], as well as advanced stages of breast cancer[59].

| Solid tumors                        | Location                        | Ref. |
|------------------------------------|---------------------------------|------|
| Glionea, Oligodendroglionea,      | Brain                           | [6,10,13] |
| Glioblastoma                       |                                 |      |
| Squamous cell carcinoma of the     | Head and neck                   | [8,22,42] |
| head and neck                      |                                 |      |
| Lung cancer (small cell carcinoma) | Lung                            | [50,134] |
| Breast cancer                      | Breast                          | [48,134] |
| Colorectal cancer                  | Colon                           | [51,135] |
| Kidney tumor                       | Kidney                          | [52,134] |
| Hepatocellular carcinoma           | Liver                           | [53,136] |
| Ovarian tumor, endometrial cancer  | Ovary                           | [54,135,136,138] |
| Primary prostate cancer            | Prostate                        | [55,134] |
| Metastatic prostate cancer         |                                 |      |
| Papilloma thyroid carcinoma,       | Thyroid                         | [56,136] |
| thryoid tumor                      |                                 |      |
| Extracellular myxoid-chondrosarcoma| Bone                            | [57]  |
| Multiple myeloma                   | Bone marrow                     | [58,137] |
| Hodgkin’s lymphoma                 | Lymph node                      | [59]  |
| Malignant melanoma                 | Melanocyte                      | [60,140] |
| Myxoid liposarcoma                 | Fat cells                       | [61]  |

**A POSSIBLE BIOLOGICAL ROLE OF CHI3L1 IN ONCOGENIC PROGRAMMING PROCESS**

It has been predicted that CHI3L1 can have a growth
stimulating effect since a family of CHI3L molecules in the fruit fly Drosophila melanogaster regulates the growth of imaginal disc cells [74]. Two of the major biological functions of CHI3L1 are a growth stimulating effect on connective tissue cells [39,72] and a potent migration enhancing effect for endothelial cells [73]. CHI3L1 also stimulates angiogenesis and reorganization of vascular endothelial cells [75]. Insulin-like growth factor-1 is a well-characterized growth factor in connective tissue cells, and works synergistically with CHI3L1 to enhance the response of human synovial cells isolated from patients with osteoarthritis [39]. In addition, CHI3L1 strongly promotes the activation of 2 major signaling pathways associated with mitogenesis and cell survival: MAPK (mitogen-activated protein kinase) pathways and PI-3K (phosphoinositide 3-kinase)-mediated pathways in fibroblast cells. The putative cell surface receptor and/or adaptive molecule for CHI3L1 are still unidentified, but the purified human CHI3L1 molecule efficiently leads to phosphorylation of MAPK p42/p44 in human synovial cells, fibroblasts, articular chondrocytes [39] and human colonic epithelial cells (Mizoguchi E, unpublished observation) in a dose-dependent manner. It has been suggested that guanine nucleotide-binding protein (G-protein)-regulated MAPK networks are involved in the action of most non-nuclear oncogenes and subsequent carcinogenesis and tumor progression [77]. The networks are involved in the activation of MAPK p42/p44 which may enhance the carcinogenic change of epithelial cells during upregulated CHI3L1 expression under inflammatory conditions.

It is believed that IBD is a risk factor of cancer development based on the severity of the disease course. As previously reported, serum CHI3L1 concentration is elevated in patients with IBD [41] and primary colorectal cancer [28]. People with CD have a 5.6-fold increased risk of developing colon cancer [78]; therefore screening for colon cancer by colonoscopy is strongly recommended for patients who have had CD for several years [78]. Inflammation was recently recognized as an important factor in the pathogenesis of malignant tumors [10] and we summarize some examples of inflammation-mediated carcinogenesis in Table 3. Of interest, most of the diseases listed in Table 3 express CHI3L1 during the course of inflammation and the subsequent tumorigenesis. CHI3L1 protects cancer cells from undergoing apoptosis and also has an effect on extracellular tissue remodeling by binding specifically with collagen types I, II, and III [82]. Therefore, CHI3L1 is strongly associated with cell survival and cell migration during the drastic tissue remodeling processes by interacting with extracellular matrix components [83,84].

The canonical (Wnt/β-catenin) pathway is known to play a crucial role in UC-related tumor progression [82]. Recently, our group identified that the SW480 human colon cancer cell line shows significantly upregulated expression and trans-nucleic translocation of β-catenin after extensive stimulation with low dose (50 ng/mL) purified CHI3L1 protein (Quidel, San Diego, CA) (Figure 1). This result strongly suggests that CHI3L1 may have a direct but not a secondary role for inflammation-associated tumorigenesis by continuously activating the Wnt/β-catenin canonical signaling pathway in CECs. As previously demonstrated, CHI3L1 expression is enhanced by proinflammatory cytokine interleukin-6 [10,83], which also has a critical tumor-promoting effect during early colitis-associated cancer tumorigenesis [84]. It has been proven that

| Table 3 Inflammation-associated carcinogenic change |
|-----------------------------------------------|
| Inflammatory disorder   | Carcinogenic formation | Ref. |
|--------------------------|------------------------|------|
| Human papillomavirus infection | Cervical carcinoma | [188-202] |
| Crohn’s disease, ulcerative colitis | Colorectal carcinoma | [115-138] |
| Chronic cholecystitis | Gall bladder carcinoma | [139-150] |
| Hepatitis B, C infection | Hepatocellular carcinoma | [151-154] |
| Asbestosis, asthma, C. pneumoniae infection, chronic obstructive lung disease, middle lobe syndrome, silicosis | Lung carcinoma | [155-167] |
| Pelvic inflammatory disease | Ovarian carcinoma | [175-177] |
| Chronic pancreatitis | Pancreatic carcinoma | [178-180] |
| H pylori infected gastritis | Gastric carcinoma, lymphoma | [181-184] |
| Chronic cystitis, schistosomiasis | Bladder carcinoma | [185-187] |
| Primary sclerosing cholangitis | Cholangio carcinoma, colorectal carcinoma, liver carcinoma, pancreatic carcinoma | [188-190] |

Figure 1 Activation of β-catenin in colonic epithelial cells by purified Chitinase 3-like-1 (CHI3L1). SW480 human colon cancer cells were cultured without (A) or with purified human CHI3L1 protein (50 ng/mL) for 24 h (B), and cells were stained with mouse anti-human β-catenin monoclonal antibody followed by FITC-horse anti-mouse IgG staining. Purified CHI3L1 significantly stimulates the nucleic translocation of β-catenin in SW480 cells. Original magnification, objective 40 x.
activation of gp130/STAT3 transcription factor regulates cell cycle progression as well as survival of enterocytes during chronic colitis-associated tumor promotion[65-68]. Therefore, the blocking of interleukin-6 mediated CHI3L1 expression by anti-CHI3L1 specific antibody or pan-family 18 chitinase inhibitors including allosamidin and methylxanthine derivatives (e.g. theophylline, caffeine, and pentoxifylline)[14,89,90] would be a useful strategy in preventing both chronic mucosal inflammation and the subsequent inflammation-associated carcinogenic change in epithelial cells. In summary, CHI3L1 could be a useful and attractive target for potential anti-cancer therapies, in particular against highly invasive and metastatic solid tumors.

**CONCLUSION**

Mammalian chitinases, including CHI3L1 and AMCase, actively participate in the pathogenesis of acute and chronic inflammation and presumably the following inflammation-associated tumorigenesis. Further understanding of the biological and physiological functions of mammalian chitinases would be very important to develop novel anti-inflammatory as well as anti-cancer therapies for several inflammatory disorders and inflammation-associated cancers in the near future.

**ACKNOWLEDGMENTS**

The authors are grateful to Dr. Atsushi Mizoguchi, Dr. Hirotohi Kikuchi, Dr. Mayumi Kawada and Dr. Chun-Chuan Chen for their helpful discussions. We would like to thank Mr. Terry D Lott and Mr. Jiang Zhang for their excellent assistance in preparing this manuscript. Segawa M is a recipient of a Student Research Fellowship Award from the Crohn's and Colitis Foundation of America Inc.

**REFERENCES**

1. Herrera-Estrella A, Chet I. Chitinases in biological control. EXS 1999; 87: 171-184
2. Rejman JJ, Hurley WL. Isolation and characterization of a novel 39 kilodalton whey protein from bovine mammary secretions collected during the nonlactating period. Biochem Biophys Res Commun 1988; 150: 329-334
3. Hakala BE, White C, Recklies AD. Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family. J Biol Chem 1993; 268: 25803-25810
4. Johansen JS, Cintin C, Jørgensen M, Kambly C, Price PA. Serum YKL-40: a new potential marker of prognosis and location of metastases of patients with recurrent breast cancer. Eur J Cancer 1995; 31A: 1437-1442
5. Shackelton LM, Mann DM, Millis 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: 13076-13083
6. Hu B, Trinh K, Figueira WF, Price PA. Isolation and sequence of a novel human chondrocyte protein related to mammalian members of the chitinase protein family. J Biol Chem 1996; 271: 19415-19420
7. Perrakis A, Tews I, Dauter Z, Oppenheim AB, Chet I, Wilson KS, Vorgias CE. Crystal structure of a bacterial chitinase at 2.3 A resolution. Structure 1994; 2: 1169-1180
8. van Aalten DM, Komander D, Snytnad B, Gaseidnes S, Peter MG, Elsijink VG. Structural insights into the catalytic mechanism of a family 18 exo-chitinase. Proc Natl Acad Sci USA 2001; 98: 8879-8984
9. Sun YJ, Chang NC, Hung SJ, Chang AC, Chou CC, Hsiao CD. The crystal structure of a novel mammalian lectin, Ym1, suggests a saccharide binding site. J Biol Chem 2001; 276: 17507-17514
10. Mizoguchi E. Chitinase 3-like-1 exacerbates intestinal inflammation by enhancing bacterial adhesion and invasion in colonic epithelial cells. Gastroenterology 2006; 130: 398-411
11. Kawada M, Chen CC, Arihiro A, Nagatani K, Watanabe T, Mizoguchi E. Chitinase 3-like-1 enhances bacterial adhesion to colonic epithelial cells through the interaction with bacterial chitin-binding protein. Lab Invest 2008; 88: 883-895
12. Rathcke CN, Johansen JS, Vestergaard H. YKL-40, a biomarker of inflammation, is elevated in patients with type 2 diabetes and is related to insulin resistance. Inflamm Res 2006; 55: 53-59
13. HogenEsch H, Dunham A, Seymour R, Renninger M, Sundberg JP. Expression of chitinase-like proteins in the skin of chronic proliferative dermatis (cpdm/cpdm) mice. Exp Dermatol 2006; 15: 808-814
14. 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: 1678-1682
15. Chupp GL, Lee CG, Janjour N, Shim YM, Holm CT, He S, Dzura JD, Reed J, Coyle AJ, Kiener P, Cullen M, Grandsaigne M, Dombret MC, Aubier M, Pretolani M, Elias JA. A chitinase-like protein in the lung and circulation of patients with severe asthma. N Engl J Med 2007; 357: 2016-2027
16. Lee CG, Hartl D, Lee GR, Koller B, Matsuura H, Da Silva CA, Sohn MH, Cohn L, Homer RJ, Kozich AA, Humbles A, Kearley J, Coyle A, 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: 1149-1166
17. Nishihkwa KC, Millis AJ. gp38k (CHI3L1) is a novel adhesion and migration factor for vascular cells. Exp Cell Res 2003; 287: 79-87
18. 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
19. Volck B, Ostergaard K, Johansen JS, Garbarsch C, Price PA. The distribution of YKL-40 in osteoarthritic and normal human articular cartilage. Scand J Rheumatol 1999; 28: 171-179
20. Cintin C, Johansen JS, Christensen IJ, Price PA, Sørensen S, Nielsen HJ. High serum YKL-40 level after surgery for colorectal carcinoma is related to short survival. Cancer 2002; 95: 267-274
21. Jensen BV, Johansen JS, Price PA. High levels of serum HER-2/neu and YKL-40 independently reflect aggressiveness of metastatic breast cancer. Clin Cancer Res 2003; 9: 4423-4434
22. Johansen JS, Drivsholm L, Price PA, Christensen IJ. High serum YKL-40 level in patients with small cell lung cancer is related to early death. Lung Cancer 2004; 46: 333-340
23. Brasso K, Christensen IJ, Johansen JS, Teisner B, Garnero P, Price PA, Iversen P. Prognostic value of PINP, bone alkaline phosphatase, CTX-I, and YKL-40 in patients with metastatic prostate carcinoma. Prostate 2006; 66: 503-513
24. Debono M, Gordee RS. Antibiotics that inhibit fungal cell wall development. Annu Rev Microbiol 1994; 48: 471-497
25. Donnelly LE, Barnes PJ. Acidic mammalian chitinase--a potential target for asthma therapy. Trends Pharmacol Sci 2004; 25: 509-511
26. Siaens R, Elsijink VG, Dierckx R, Slegers G. (123)I-Labeled chitinase as specific radioligand for in vivo detection of fungal infections in mice. J Nucl Med 2004; 45: 1209-1216
27. Hollak CE, van Weely S, van Oers MH, Aerts JM. Marked
elevation of plasma chitotriosidase activity. A novel hallmark of Gaucher disease. J Clin Invest 1994; 93: 1288-1292

28 Boven LA, van Meurs M, Boot RG, Mehta A, Boon L, Aerts JM, Laman JD. Gaucher cells distinguish a distinct macrophage phenotype and resemble alternatively activated macrophages. Am J Pathol 2004; 122: 359-369

29 Aguilar B, Ghauchari-van der Vlugt K, Helmond MT, Ot JM, Donker-Koopman WE, Groener JE, Boot RG, Renkema GH, van der Mare GA, van Boom JH, Overkleeft HS, Aerts JM. Transglycosidase activity of chitotriosidase: improved enzymatic assay for the human macrophage chitinase. J Biol Chem 2002; 277: 40911-40916

30 Barone R, Brurberg M, Musumeci S. Plasma chitotriosidase in health and pathology. Clin Lab 2007; 53: 321-333

31 Boot RG, Renkema GH, Verhoek M, Strijland A, Blek J, de Meulemeester TM, Mannens MM, Aerts JM. The human chitotriosidase gene. Nature of inherited enzyme deficiency. J Biol Chem 1998; 273: 25680-25685

32 Choi EH, Zimmerman PA, Foster CB, Zhu S, Kumarsawami V, Nutman TB, Chanock SJ. Genetic polymorphisms in molecules of innate immunity and susceptibility to infection with Wuchereria bancrofti in South India. Genes Immun 2001; 2: 248-253

33 Boot RG, Renkema GH, Strijland A, van Zonneveld AJ, Aerts JM. Cloning of a cDNA encoding chitotriosidase, a human chitiniase produced by macrophages. J Biol Chem 1995; 270: 26252-26256

34 Fusetti F, von Moeller H, Houston D, Rozeboom HJ, Dijkstra BV, Boot RG, Aerts JM, van Ommen GB. Structure of human chitotriosidase. Implications for specific inhibitor design and function of mammalian chitinase-like lectins. J Biol Chem 2002; 277: 25537-25544

35 Davies GJ, Mackenzie L, Varrot A, Dauter M, Brzozowski A. Snapshots along an enzymatic pathway for the human chitinase produced by macrophages. J Biol Chem 2001; 276: 6770-6776

36 Elias JA, Homer RJ, Hamid Q, Lee CG. Chitinases and chitinase-like proteins in T(H)2 inflammation and asthma. J Allergy Clin Immunol 2005; 116: 497-500

37 Ober C, Tan Z, Sun Y, Possick JD, Pan L, Nicolae R, Radford S, Parry RR, Hein zumann A, Diechmann KA, Lester LA, Germ JE, Lemanske RB Jr, Nicolae DL, Elias JA, Chupp GL. Effect of variation in CHI3L1 on serum YKL-40 level, risk of asthma, and lung function. N Engl J Med 2008; 358: 1682-1691

38 Recklies AD, White C, Ling H. The chitinase 3-like protein human cartilage glycoprotein 39 (HC-gp-39) stimulates proliferation of human connective-tissue cells and activates both extracellular signal-regulated kinase- and protein kinase B-mediated signalling pathways. Biochem J 2002; 365: 119-126

39 Ling H, Recklies AD. The chitinase 3-like protein human cartilage glycoprotein 39 inhibits cellular responses to the inflammatory cytokines interleukin-1 and tumour necrosis factor-alpha. Biochem J 2004; 380: 651-659

40 Vind I, Johansen JS, Price PA, Munkholm P. Serum YKL-40, a potential new marker of disease activity in patients with inflammatory bowel disease. Scand J Gastroenterol 2003; 38: 599-606

41 Johansen JS, Møller S, Price PA, Bendtsen F, Junge J, Garbarsch C, Henriksen JH. Plasma YKL-40: a new potential marker of fibrosis in patients with alcoholic cirrhosis? Scand J Gastroenterol 1997; 32: 582-590

42 Rehli M, Niller HH, Ammon C, Langmann S, Schwarzfischer L, Andreesen R, Krause SW. Transcriptional regulation of CHI3L1, a marker gene for late stages of macrophage differentiation. J Biol Chem 2003; 278: 44084-44097

43 van Bilsen JH, van Dongen H, Lard LR, van der Voort El, Efferink DG, Bakker AM, Miltenburg AM, Huitzenga TW, de Vries RR, Toes RE. Functional regulatory immune responses against human cartilage glycoprotein-39 in health vs. proinflammatory responses in rheumatoid arthritis. Proc Natl Acad Sci USA 2004; 101: 17180-17185

44 Johansen JS, Aerts JM, Meijerink JH, Price PA. A new biochemical marker for joint injury. Analysis of YKL-40 in serum and synovial fluid. Br J Rheumatol 1993; 32: 949-955

45 Verheijden GF, Rijnders AW, Bos E, Coenen-de Roo CJ, van Staveren CJ, Miltenburg AM, Meijerink JH, Elewaut D, de Keyser F, Veys E, Boots AM. Human cartilage glycoprotein-39 as a candidate autoantigen in rheumatoid arthritis. Arthritis Rheum 1997; 40: 1115-1125

46 Eriksson K, Holmgren J. Recent advances in mucosal vaccines and adjuvants. Curr Opin Immunol 2002; 14: 666-672

47 Iweala OI, Nagler CR. Immune privilege in the gut: the establishment and maintenance of non-responsiveness to dietary antigens and commensal flora. Immunol Rev 2006; 213: 82-100

48 Wolters DA, Coenen-de Roo CJ, Mebius RE, van der Cannen MJ, Tirion F, Miltenburg AM, Kraal G. Intranasally induced immunological tolerance is determined by characteristics of the draining lymph nodes: studies with OVA and human cartilage gp-39. J Immunol 1999; 162: 1994-1998

49 Joosten LA, Coenen-de Roo CJ, Helsen MM, Lubberts E, Boots AM, van den Berg WB, Miltenburg AM. Induction of tolerance with intranasal administration of human cartilage gp-39 in DBA/1 mice: amelioration of clinical, histologic, and radiologic signs of type II collagen-induced arthritis. Arthritis Rheum 2000; 43: 645-655

50 Zandbelt MM, Houbiers JG, van den Hoogen FH, Meijerink J, van Riel PL, in’t Hout J, van de Putte LB. Intranasal administration of recombinant human cartilage glycoprotein-39. A phase I escalating cohort study in patients with rheumatoid arthritis. J Rheumatol 2006; 33: 1726-1733

51 Darfeuille-Michaud A, Bouteau J, Bulois P, Neut C, Glasser AL, Barnich N, Bringer MA, Swidsinski A, Beaugerie L, Colombel JF. High prevalence of adherent-invasive Escherichia coli associated with ileal mucosa in Crohn’s disease. Gastroenterology 2004; 127: 412-421

52 Swidsinski A, Ladhoff A, Pernthaler A, Swidsinski S, Loening-Baucke V, Ortner M, Weber J, Hoffmann U, Schreiber S, Dietel M, Lochs H. Mucosal flora in inflammatory bowel disease. Gastroenterology 2002; 122: 44-54

53 Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature 2007; 448: 427-434

54 Dehn H, Høgdall EV, Johansen JS, Jørgensen M, Price PA, Engelholm SA, Høgdall CK. Plasma YKL-40, as a prognostic tumor marker in recurrent ovarian cancer. Acta Obstet Gynecol Scand 2003; 82: 287-293

55 Høgdall EV, Ringholt M, Høgdall CK, Christensen IJ, Johansen JS, Kjaer SK, Blaaaker J, Ostenfeld-Møller L, Price PA, Christensen LH. YKL-40 tissue expression and plasma levels in patients with ovarian cancer. BMC Cancer 2009; 9: 8

56 Johansen JS, Christensen IJ, Riisbro R, Greenall M, Han C, Price PA, Smith K, Brünner N, Harris AL. High serum YKL-40 levels in patients with primary breast cancer is related to short recurrence free survival. Breast Cancer Res Treat 2003; 80: 15-21

57 Mitsuhashi A, Matsui H, Ushii H, Nagai Y, Tate S, Unno Y, Hirashiki K, Seki K, Shouz M. Serum YKL-40 as a marker for cervical adenocarcinoma. Ann Oncol 2009; 20: 71-77

58 Coskun U, Yamac D, Gulbahar O, Sancak B, Karaman N, Ozkan S. Locally advanced breast carcinoma treated with neoadjuvant chemotherapy: are the changes in serum levels of YKL-40, MMP-2 and MMP-9 correlated with tumor response? Neoplasma 2007; 54: 348-352

59 Gronlund B, Høgdall EV, Christensen IJ, Johansen JS, Nærgaard-Pedersen B, Engelholm SA, Høgdall C. Pre-treatment prediction of chemoresistance in second-line chemotherapy of ovarian carcinoma: value of serological tumor marker determination (tetranection, YKL-40, CASA, ...
Diefenbach CS, Shah Z, Iasonos A, Barakat RR, Levine DA, Aghajanian C, Sabatinpi, P, Hensley ML, Konner J, Tew W, Spriggs D, Fleisher M, Thaler H, Dupont J. Preoperative serum levels of YKL-40 as a marker for detection of endometrial cancer. Gynecol Oncol 2007; 104: 435-442

Roslund A, Johansen JS, Christensen IJ, Kiss K, Balslev E, Nielsen DL, Bentzen J, Price PA, Andersen E. High serum levels of YKL-40 in patients with squamous cell carcinoma of the head and neck are associated with short survival. Int J Cancer 2008; 122: 857-863

Johansen JS, Brasso K, Iversen P, Teisbørn B, Garnepa P, Price PA, Christensen IJ. Changes of biochemical markers of bone turnover and YKL-40 following hormonal treatment for metastatic prostate cancer are related to survival. Clin Cancer Res 2007; 13: 3244-3249

Schmidt H, Johansen JS, Gehr H, Geertsen PF, Fode K, van der Maase H. Elevated serum level of YKL-40 is an independent prognostic factor for poor survival in patients with metastatic melanoma. Cancer 2006; 106: 1130-1139

Biggar RJ, Johansen JS, Smedby KE, Rostgaard K, Chang ET, Adami H, Glimelius B, Molin D, Hamilton-Dutoit S, Melbye M, Hjalgrim H. Serum YKL-40 and interleukin 6 levels in Hodgkin lymphoma. Clin Cancer Res 2008; 14: 6974-6978

Johansen JS, Bojesen SE, Myllin AK, Frikke-Schmidt R, Price PA, Nordestgaard BG, Andersen E. High serum levels of YKL-40 in patients with squamous cell carcinoma of the head and neck are associated with short survival. Int J Cancer 2008; 122: 857-863

Qin W, Zhu W, Schlatter L, Mickle R, Loy TS, Atsasoy U, Hewett JE, Sauter ER. Increased expression of the inflammatory protein YKL-40 in precancers of the breast. Int J Cancer 2007; 121: 1536-1542

Johansen JS, Pedersen AN, Schroll M, Jørgensen T, Pedersen BK, Brunsgård H. High serum YKL-40 level in a cohort of octogenarians associated with increased risk of all-cause mortality. Clin Exp Immunol 2008; 151: 260-266

Rehli M, Krause SW, Andreesen R. Molecular characterization of the gene for human cartilage gp-39 (CHI3L1), a member of the chitinase protein family and marker for late stages of macrophage differentiation. Genomics 1997; 43: 221-225

Krause SW, Rehli M, Kreutz M, Schwarzliff L, Paulauskis JD, Andreesen R. Differential screening identifies genetic markers of monocyte to macrophage maturation. J Lipids Res 1996; 40: 540-545

Volck B, Price PA, Johansen JS, Serensen 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 neutrophils. Proc Assoc Am Physicians 1998; 110: 351-360

De Ceninck F, Gauffilier S, Bonnau A, Sabatini M, Lerca S, Pastoureau P. YKL-40 (cartilage gp-39) induces proliferative events in cultured chondrocytes and synoviocytes and increases glycosaminoglycan synthesis in chondrocytes. Biochim Biophys Acta Commun 2001; 285: 926-931

Malinda KM, Ponce L, Kleinman HK, Shackelton LM, Millis AJ. Gp38k, a protein synthesized by vascular smooth muscle cells, stimulates directional migration of human umbilical vein endothelial cells. Exp Cell Res 1999; 240: 168-173

Nigro JM, Misra A, Zeng L, Strimov I, Colman H, Griffin C, Ochsenb N, Chen M, Pan E, Koal D, Yung WK, Weissman BE, Aldape KD. Integrated array-comparative genomic hybridization and expression array profiles identify clinically relevant molecular subtypes of glioblastoma. Cancer Res 2005; 65: 1678-1686

Roslund A, Johansen JS, Junker N, Nielsen DL, Dzaferi H, Price PA, Balslev E. YKL-40 expression in benign and malignant lesions of the breast: a methodologic study. Appl Immunohistochem Mol Morphol 2007; 15: 371-381

Kawamura K, Shibata T, Saito O, Peo D, Bryant PY. A new family of growth factors produced by the fat body and active on Drosophila imaginal disc cells. Development 1999; 126: 211-219

Pearson G, Robinson F, Beers Gibson T, Xu BE, Karandikar M, Berman K, Cobb MH. Mitogen-activated protein (MAP) kinase pathway and progression and physiological functions. Endocr Rev 2001; 22: 153-183

Ekbom A, Helwick C, Zack M, Adami HO. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. Lancet 1990; 336: 357-359

Collins PD, Mpouf C, Watson AJ, Rhodes J. Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. Cochrane Database Syst Rev 2006; CD000729

Bromberg J, Wang TC. Inflammation and cancer: IL-6 and STAT3 complete the link. Cancer Cell 2009; 15: 79-80

Bigg HF, Wait R, Rowan AD, Pawson TE. The mammalian chitinase-like lectin, YKL-40, binds specifically to type I collagen and modulates the rate of type I collagen fibril formation. J Biol Chem 2006; 281: 21082-21095

van Dekken H, Wink JC, Vissers KJ, Franken PF, Ruud Schouten W, J Hop WC, Kuipers EJ, Fodde R, Janneke van der Woude C. Wnt pathway-related gene expression during malignant progression in ulcerative colitis. Acta Histochem 2007; 109: 266-272

De Ceninck F, Pastoureau P, Bouet F, Bonnet J, Vanhoutte PM. Purification of guinea pig YKL40 and modulation of its secretion by cultured articular chondrocytes. J Cell Biochem 1998; 69: 414-424

Grivennikov S, Karin E, Torzic J, Mucida D, Yuan YG, Vallabhappurapu S, Scheller J, Rose-John S, Chouart R, Eckmann L, Karin M. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell 2009; 15: 103-113

Bollrath J, Phese TJ, von Burstin VA, Patučzki T, Bennecke M, Bateman T, Nebelsiek T, Lundgren-May T, Canli O, Schiwatalla S, Matthews V, Schimid RM, Kirchner T, Arkan MC, Ernst M, Greeten FR, gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. Cancer Cell 2009; 15: 91-102

Atreya R, Neurath MF. Signaling molecules: the pathogenic role of the IL-6/STAT3 trans signaling pathway in intestinal inflammation and in colonic cancer. Curr Drug Targets 2008; 9: 369-374

Atreya R, Neurath MF. Involvement of IL-6 in the pathogenesis of inflammatory bowel disease and cancer. Curr Rev Allergy Immunol 2005; 28: 187-196

Han X, Somoswarsa D, Bonkowski EL, Denson LA. Growth hormone inhibitors signal transducer and activator of transcription 3 activation and reduces disease activity in murine colitis. Gastroenterology 2005; 129: 185-203

Bucolo C, Musumeci M, Maltese A, Drago F, Musumeci S. Effect of chitinase inhibitors on endotoxin-induced uveitis (EIU) in rabbits. Pharmacol Res 2008; 57: 247-252

Rao FV, Andersen OA, Vora KA, Demartino JA, van Aalten DM. Methylxanthine drugs are chitinase inhibitors: investigation of inhibition and binding modes. Chem Biol 2005; 12: 973-980

Kronborg G, Ostergaard C, Weis N, Nielsen H, Obel N, Pedersen SS, Price PA, Johansen JS. Serum level of YKL-40 is elevated in patients with Streptococcus pneumoniae bacteremia and is associated with the outcome of the disease. Scand J Infect Dis 2002; 34: 322-326

Nordenbaek C, Johansen JS, Junker P, Borregaard N, Serensen O, Price PA. YKL-40, a matrix protein of specific granules in neutrophils, is elevated in serum of patients with community-acquired pneumonia requiring hospitalization. J Infect Dis 1999; 180: 1722-1726

Létuve S, Kozhich A, Arouche N, Grandsaigne 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.
Immunol 2008; 181: 5167-5173

94 Sanders NN, Eijssink VG, van den Pangaart PS, Joost van Neerven RJ, Simors PJ, De Smedt SC, Demester J. Muricolytic activity of bacterial and human chitinases. Biochim Biophys Acta 2007; 1770: 858-866

95 Ramanathan M Jr, Lee WK, Lane AP. Increased expression of acidic mammalian chitinase in chronic rhinosinusitis with nasal polyps. Am J Rhinol 2006; 20: 330-335

96 Tercelj M, Salobir B, Simic S, Wraber B, Zupancic M, Rylander R. Chitotriosidase activity in sarcoidosis and some other pulmonary diseases. Scand J Clin Invest 2009; 69: 575-578

97 Brunner J, Scholl-Bürghi S, Prelog M, Zimmerhackl LB. Chitotriosidase as a marker of disease activity in sarcoidosis. Rheumatol Int 2007; 27: 1185-1186

98 Coffman MD. Chitinase 3-Like-1 (CHI3L1): a putative disease marker at the interface of proteomics and glycomics. Crit Rev Clin Lab Sci 2008; 45: 531-562

99 Østergaard C, Johansen JS, Benfield T, Price PA, Lundgren JD. YKL-40 is elevated in cerebrospinal fluid from patients with purulent meningitis. Clin Diug Imn Immunol 2002; 9: 598-604

100 Bonneh-Barkay D, Bissel SJ, Wang G, Fish KN, Nicholl GC, Darko SW, Medina-Flores R, Murphrey-Cor B, Rajakumar PA, Nyaundi J, Mellers JW, Bowser R, Wiley CA. YKL-40, a marker of simian immunodeficiency virus encephalitis, modulates the biological activity of basic fibroblast growth factor. Am J Pathol 2008; 173: 150-143

101 Pozzuoli A, Valvasor C, Bernardi D, Plebani M, Fabris Montemurici D, Candiotti S, Aldegeri R, Punzi L. YKL-40 in human lumbar herniated disc and its relationships with nitric oxide and cyclooxygenase-2. Clin Exp Rheumatol 2007; 25: 453-456

102 Brunner JK, Scholl-Bürghi S, Hössinger D, Wondrak P, Prelog M, Zimmerhackl LB. Chitotriosidase activity in juvenile idiopathic arthritis. Rheumatol Int 2008; 28: 949-950

103 Johansen JS, Hvalres J, Hansen M, Bækker V, Lorenzen L, Price PA. Serum YKL-40 levels in healthy children and adults. Comparison with serum and synovial fluid levels of YKL-40 in patients with osteoarthritis or trauma of the knee joint. Br J Rheumatol 1996; 35: 553-559

104 Huang K, Wu LD. YKL-40: a potential biomarker for osteoarthritis. J Int Med Res 2009; 37: 18-24

105 Cook EB. Tear cytokines in acute and chronic allergic ocular inflammation. Curr Opin Allergy Clin Immunol 2004; 4: 441-445

106 Musumeci M, Bellin M, Maltese A, Aragona P, Bucolo C, Musumeci S. Chitinase levels in the tears of subjects with ocular allergies. Cornea 2008; 27: 168-173

107 Takahashi S, Wang TC. Gene expression profiling in a mouse model of Helicobacter-induced gastric cancer. Cancer Sci 2007; 98: 284-293

108 Cozzarini E, Bellin M, Norberto L, Pulese L, Musumeci S, Lanfranchi G, Paolotti MG, CHI3L1 and AMCase expression in human gastric mucosa: correlation with inflammation and Helicobacter pylori infection. Eur J Gastroenterol Hepatol 2009; 21: 1119-1126

109 Koutroubakis IE, Petinaki E, Dimoulis P, Vardas E, Rousopoulos A, Marinaki A, Kouroumalis EA. Increased serum levels of YKL-40 in patients with inflammatory bowel disease. Int J Coloproctol Dis 2005; 20: 254-259

110 Neijgaard C, Hest NB, Christensen JJ, Poulsen SH, Egstrup K, Price PA, Johansen JS. Serum levels of YKL-40 increases in patients with acute myocardial infarction. Coron Artery Dis 2008; 19: 257-263

111 Wang Y, Ripa RS, Johansen JS, Gabrielsen A, Steinbruchel DA, Fries T, Bindseil L, Haack-Sørensen M, Jørgensen E, Kastrup J. YKL-40 a new biomarker in patients with acute coronary syndrome or stable coronary artery disease. Scand Cardiovasc Dis 2006; 42: 295-302

112 Troidl C, Möllmann H, Nef H, Masseli F, Voss S, Szardien S, Willmer M, Rolf A, Rixe J, Troidl K, Kostin S, Hamm C, Elsässer A. Classically and alternatively activated macrophages contribute to tissue remodelling after myocardial infarction. J Cell Mol Med 2009; Epub ahead of print

113 Boot RG, van Achterberg TA, van Aken BE, Renkema GH, Jacobs MJ, Aerts RJ, de Voogt J. Strong induction of members of the chitinase family of proteins in atherosclerosis: chitinase-3-like-1 and human cartilage gp-39 expressed in lesional macrophages. Arterioscler Thromb Vasc Biol 1999; 19: 679-694

114 Shackell NA, McGuinness PH, Abbott CA, Gorrell MD, McCaughan GW. Novel differential gene expression in human cirrhosis detected by suppression subtractive hybridization. Hepatology 2003; 38: 577-588

115 Berres ML, Papen S, Pauels K, Schmitz P, Zaldarov MM, Hellerbrand C, Mueller T, Berg T, Weiskirchen R, Trautwein C, Wasmuth HE. A functional variation in CHI3L1 is associated with severity of liver fibrosis and YKL-40 serum levels in chronic hepatitis C infection. J Hepatol 2009; 50: 370-376

116 Malaguarnera L, Rosa MD, Zambito AM, dell’Ombra N, Marco RD, Malaguarnera M. Potential role of chitinotrasidase gene in nonalcoholic fatty liver disease evolution. Am J Gastroenterol 2006; 101: 2060-2069

117 Malaguarnera L, Di Rosa M, Zambito AM, dell’Ombra N, Niccoliti F, Malaguarnera M. Chitotriosidase gene expression in Kupffer cells from patients with non-alcoholic fatty liver disease. Gut 2006; 55: 1313-1320

118 Johansen JS, Christoffersen P, Møller S, Price PA, Henriksen JH, Garbarsch C, Bendtsen F. Serum YKL-40 is increased in patients with hepatic fibrosis. J Hepatol 2000; 32: 911-920

119 Van Steijn GJ, Amerongen AV, Veerman EC, Kasanmoantalib S, Overdijk B. Effect of periodontal treatment on the activity of chitinase in whole saliva of periodontitis patients. J Periodont Res 2002; 37: 245-249

120 Van Steijn GJ, Amerongen AV, Veerman EC, Kasanmoantalib S, Overdijk B. Chitinase in whole and glandular human salivas and in whole saliva of patients with periodontal inflammation. Eur J Oral Sci 1999; 107: 328-337

121 Nordenbaek C, Johansen JS, Halberg P, Wiik A, Garbarsch C, Ullman S, Price PA, Jacobsen S. High serum levels of YKL-40 in patients with systemic sclerosis are associated with pulmonary involvement. Scand J Rheumatol 2005; 34: 293-297

122 La Montagna G, D’Angelo S, Valenti G. Cross-sectional evaluation of YKL-40 serum concentrations in patients with systemic sclerosis. Relationship with clinical and serological aspects of disease. J Rheumatol 2003; 30: 2147-2151

123 Lal A, Lash AE, Altschul SF, Velculescu V, Zhang L, McLendon RE, Marra MA, Prange C, Morin PJ, Polyak K, Papadopoulos N, Vogelstein B, Kinzler KW, Strausberg RL, Riggins GJ. A public database for gene expression in human cancers. Cancer Res 1999; 59: 5403-5407

124 Markert JM, Parker JN, Gillespie GY, Whitley R. Genetically engineered human herpes simplex virus in the treatment of brain tumours. Herpes 2001; 8: 17-22

125 Tanwar MK, Gilbert MR, Holland EC. Gene expression microarray analysis reveals YKL-40 to be a potential serum marker for malignant character in human glioma. Cancer Res 2002; 62: 4364-4368

126 Nutter CL, Betensky RA, Brower MA, Batchelor TT, Louis DN, Stemmer-Rachamimov AO. YKL-40 is a differential diagnostic marker for histologic subtypes of high-grade gliomas. Clin Cancer Res 2005; 11: 2258-2264

127 Pellonki CE, Mahajan A, Maor M, Chang EL, Woo S, Gilbert M, Colman H, Yang H, Ledoux A, Blair H, Passe S, Jenkins RB, Aldape KD. YKL-40 expression is associated with poorer response to radiation and shorter overall survival in glioblastoma. Clin Cancer Res 2005; 11: 3326-3334

128 Pellonki CE, Ballman KV, Furrth AF, Zhang L, Lin E, Sulman EP, Bhat K, McDonald JM, Yung WK, Colman H, Woo SY, Heinberger AB, Suki D, Prados MD, Chang SM, Barker FG 2nd, Buckner JC, James CD, Aldape K. Epidermal growth

www.wjgnet.com
factor receptor variant III status defines clinically distinct subtypes of glioblastoma. J Clin Oncol 2007; 25: 2288-2294.

129 Hormigo A, Gu B, Karimi S, Riedel E, Panageas KS, Edgar MA, Tanwar MK, Rao JS, Fleisher M, DeAngelis LM, Holland EC. YKL-40 and matrix metalloproteinase-9 as potential serum biomarkers for patients with high-grade gliomas. Clin Cancer Res 2006; 12: 5698-5704.

130 Rousseau A, Nutt CL, Betensky RA, Lafort A, Han M, Ligon KL, Rowitch DH, Louis DN. Expression of oligodendroglial and astrocytic lineage markers in diffuse gliomas: use of YKL-40, ApoE, ASC1L, and NFKX2-2. J Neuropathol Exp Neurol 2005; 64: 119-136.

131 Saidi A, Laverzet S, Bellahcène A, De Vos J, Bello L, Castronovo V, Deprez M, Loiseau H, Bikalvi A, Hagedorn M. Experimental anti-angiogenesis causes upregulation of genes associated with poor survival in glioblastoma. Int J Cancer 2008; 122: 2187-2198.

132 Bhat KP, Pelloski CE, Zhang Y, Kim SH, deLaCruz C, Rehli M, Aldape KD. Selective repression of YKL-40 by NF-kappaB in glioma cell lines involves recruitment of histone deacetylase-1 and -2. FEMS Lett 2008; 582: 3193-3200.

133 Johansen JS, Lottenburger T, Nielsen HJ, Jensen JE, Svendsen MN, Kollerup G, Christensen JI. Diurnal, weekly, and long-time variation in serum concentrations of YKL-40 in healthy subjects. Cancer Epidemiol Biomarkers Prev 2008; 17: 2603-2608.

134 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: 223-231.

135 Johansen JS, Jensen BY, Roslund A, Nielsen D, Price PA. Serum YKL-40, a new prognostic biomarker in cancer patients? Cancer Epidemiol Biomarkers Prev 2006; 15: 194-202.

136 Cintin C, Johansen JS, Christensen JI, Price PA, Sørensen S, Nielsen HJ. Serum YKL-40 and colorectal cancer. Br J Cancer 1999; 79: 1494-1499.

137 Morgante M, Di Munno O, Morgante D. [YKL 40: marker of disease activity in rheumatoid arthritis?] Minerva Med 1999; 90: 437-441.

138 Hogdall EV, Kjaer SK, Glud E, Christensen L, Blaakaa J, Vuust J, Bock JE, Norgaard-Pedersen B, Hogdall CK. Evaluation of a polymorphism in intron 2 of the p33 gene in ovarian cancer patients. From the Danish "Malova" Ovarian Cancer Study. Anticancer Res 2003; 23: 3397-3404.

139 Dupont J, Tanwar MK, Thaler HT, Fleisher M, Kauft N, Hensley ML, Sabattini P, Anderson S, Aghajanian C, Holland EC. Provides early detection and monitoring of serum YKL-40 and IL-6 as response biomarkers. J Immunother 2005; 28: 260-268.

140 Svane IM, Pedersen AE, Johansen JS, Johnsen HE, Nielsen D, Kamby C, Ottesen S, Ballevsle E, Gaarsdal E, Nikolajsen K, Johansen JS. Vaccination with p53 peptide-pulsed dendritic cells is associated with disease stabilization in patients with advanced breast cancer. Br J Cancer 2003; 89: 1485-1499.

141 Yamac D, Wang Y, Wen JM, Xiao G, Zhang WM, Lau GK, Yang M, Wang L, Mei R, Huang Y, Prasad M, Lemon WJ, Hampel H, Wright FA, Kornacker K, LiVolsi V, Frankel W, Kloos RT, Eng C, Pellegata NS, de la Chapelle A. Gene expression in papillary thyroid carcinoma reveals highly consistent profiles. Proc Natl Acad Sci USA 2001; 98: 15044-15049.

142 Sjögren M, Heis-Kindblom JM, Orndal C, Bergh P, Arbyn M, Sankaranarayanan R, Tsu V, Ronco Yio X. Inflammation and cancer IV. J J Pathol 2003; 162: 781-792.

143 Mylin AK, Rasmussen T, Johansen JS, Knudsen LM, Nargardh PH, Lenhoff S, Dabl IM, Johansen HE. Serum YKL-40 concentrations in newly diagnosed multiple myeloma patients and YKL-40 expression in malignant plasma cells. Eur J Haematol 2006; 77: 416-424.

144 Mylin AK, Andersen NF, Johansen JS, Abildgaard N, Heikendorff L, Standal T, Gimsing P, Knudsen LM. Serum YKL-40 and bone marrow angiogenesis in multiple myeloma. Int J Cancer 2009; 124: 1492-1494.

145 Balamurugan A, Ahmed F, Saraiya M, Coskun U, Tekin E, Sancak B, Yildiz Y, Tanwar MK, Thaler HT, Fleisher M, Kauff N, Isman FK, Balci C, Onal B, Hacibekiroglu M, Kilici M, Aldape KD. Selective repression of YKL-40 by NF-kappaB and astrocytic lineage markers in diffuse gliomas: use of fluorescent in situ hybridization. Neuro Oncol 2006; 8(Suppl 10): K29-K41.

146 Hasan UA, Bates E, Takeshita F, Bilato A, Accardi R, Bouvard V, Mansour M, Vincent I, Gissmann L, Iftner T, Sideri M, Stubenrauch F, Tommasino M. Potential role of human papillomavirus in the development of subsequent primary in situ and invasive cancers among cervical cancer survivors. Cancer 2008; 113: 2919-2925.

147 Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrand MH, Dillner J, Meijer CJ. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developing and developing countries. Vaccine 2008; 26(Suppl 10): K29-K41.

148 Mitchell H, Drake M, Medley G. Prospective evaluation of risk of cervical cancer after cytological evidence of human papillomavirus infection. Lancet 1986; 1: 573-575.

149 Ekboom A, Helmck C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 1990; 323: 1228-1233.

150 Greenstein AJ, Sachar DB, Smith H, Pucillo A, Papastass AE, Kereel I, Geller SA, Janowitz HD, Auesfes AH Jr. Cancer in universal and left-sided ulcerative colitis: factors determining risk. Gastroenterology 1979; 77: 290-294.

151 Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol 2004; 287: G7-G17.

152 Sugita A, Sachar DB, Badian C, Ribeiro MB, Auesfes AH Jr, Greenstein AJ. Colorectal cancer in ulcerative colitis. Influence of anatomical extent and age at onset on colitis-cancer interval. Gut 1991; 32: 167-169.

153 Branco BC, Harpaz N, Sachar DB, Greenstein AJ, Tabrizian P, Bauer JJ, Greenstein AJ. Colorectal carcinoma in indeterminate colitis. Inflamm Bowel Dis 2005; 11: 1076-1081.

154 Gyde SN, Prior P, Macartney JC, Thompson H, Waterhouse JA, Allan RN. Malignancy in Crohn's disease. Gut 1980; 21: 1024-1029.

155 Sachar DB. Cancer in Crohn's disease: dispelling the myths. Gut 1994; 35: 1507-1508.

156 Nagata E, Sakata K, Katsohita H, Kobayashi Y. The relation between carcinoma of the gallbladder and an anomalous connection between the choledochus and the pancreatic duct. Ann Surg 1985; 202: 182-190.

157 Yanagisawa N, Mikami T, Koike M, Okayasu I. Enhanced cell kinetics, p53 accumulation and high p21WAF1 expression in chronic cholecystitis: comparison with background mucosa of gallbladder carcinomas. Histopathology 2000; 36: 54-61.

158 Zhang M, Fan JW, Ren TR, Zhu YF, Han YJ, Kühnel W. Correlated expression of inducible nitric oxide synthase and P53, Bax in benign and malignant diseased gallbladder. Ann
