

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

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

Katrin Eurich, Mayuko Segawa, Satoko Toei-Shimizu, Emiko Mizoguchi, Gastrointestinal Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, United States

Emiko Mizoguchi, Center for the Study of Inflammatory Bowel Disease, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, United States

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Correspondence to: Emiko Mizoguchi, MD, PhD, Assistant Professor of Medicine, Gastrointestinal Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, GRJ 702, 55 Fruit Street, Boston, MA 02114, United States. emizoguchi@partners.org

Telephone: +1-617-7267892 Fax: +1-617-7263673

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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.

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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

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^[2], 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*^[17]. 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 inflammation 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. *p*-nitrophenyl chitooligosaccharides)^[29]. Subsequent studies revealed that the increased CHIT1 activity in Gaucher disease patients is associated with aberrant macrophage activation^[28], 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^[29]. 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^[36], but an exciting biological role of AMCase was revealed by Zhu *et al*^[14] 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^[37]. The same group further identified that overproduction of AMCase is highly dependent on a Th2 cytokine IL-13, which further induces production of IP-10 [interferon (IFN)-inducible protein-10] and ITAC (IFN-inducible T cell alpha chemoattractant)^[14]. 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^[14,37]. 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^[14], 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^[15]. 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^[15]. 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^[38]. 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 <i>S. pneumoniae</i>	CHI3L1	[91,92]
	Bronchial asthma	CHI3L1,	[14,38]
		AMCase, Ym1	
	COPD	CHI3L1	[93]
	Cystic fibrosis	AMCase, CHIT1	[94]
	Rhinosinusitis	AMCase	[95]
Blood	Sarcoidosis	CHIT1	[96,97]
	Bacterial septicemia	CHI3L1	[98]
Brain	Encephalitis	CHI3L1	[99,100]
	Meningitis	CHI3L1	[99]
Disc/Joint	Intervertebral disc degeneration	CHI3L1	[101]
	Juvenile idiopathic arthritis	CHIT1	[102]
	Osteoarthritis, RA	CHI3L1	[103,104]
Eye	Conjunctivitis	AMCase	[105,106]
		CHI3L1, CHIT1	[107,108]
GI tract	Helicobacter gastritis	CHI3L1	[10,109]
	Inflammatory bowel disease	CHI3L1	[10,109]
Heart	Acute myocardial infarction	CHI3L3, CHI3L1	[110,111,112]
	Coronary artery disease	CHIT1	[113]
Liver	Chronic hepatitis C, LC	CHI3L1	[114, 115]
	Fatty liver disease	CHIT1	[116,117]
	Hepatic fibrosis	CHI3L1	[118]
Oral cavity	Periodontitis	Chitinase	[119,120]
Systemic	Gaucher disease	CHIT1	[27]
	Systemic sclerosis	CHI3L1	[121,122]

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^[59]. 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*^[39] 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)]^[41], asthma^[15,38] and liver cirrhosis^[42]. Serum CHI3L1 is rarely detectable in healthy individuals^[41], and therefore CHI3L1 has recently been proposed as a useful marker for indicating inflammatory activity and poor clinical prognosis for IBD^[41]. 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)^[10,19,43]. CHI3L1 is strongly expressed by macrophages in the synovial membrane of patients with rheumatoid arthritis (RA) and a polarized IFN γ -

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 IFN γ -dominated proinflammatory phenotype^[44]. In addition, serum levels of CHI3L1 are positively correlated with the severity of arthritis^[45]. 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^[46]. 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^[46]. 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^[10]. 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^[52,53]. 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^[11]. 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^[54]. 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^[16]. 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^[16]. 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^[22], metastatic breast cancer^[57], and metastatic prostate cancer^[23]. In addition, several groups have reported that CHI3L1 is one of the most significant prognosis markers for cervical adenocarcinoma^[58], recurrent breast cancer^[4] 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^[59], ovarian carcinoma^[60], endometrial cancer^[61], squamous cell carcinoma of the head and neck^[62], metastatic prostate cancer or melanoma^[63,64], Hodgkin's lymphoma^[65] and colon cancer^[20]. Based on extensive research by Johansen and colleagues, CHI3L1 may be used as a novel and sensitive predictor of any cancer^[66,67]. They categorized patients into 5 distinct levels according to the amount of plasma CHI3L1 detected by ELISA, and found that participants with the highest level of plasma CHI3L1 had a median survival rate of only 1 year after the cancer diagnosis^[66]. In contrast, the patients with the lowest level of plasma CHI3L1 had a survival rate of more than 4 years. Although the variation of CHI3L1 serum levels in healthy subjects in this study was relatively small, subsequent measurements would be required to determine cancer risk since the serum level of CHI3L1 could also be elevated in patients with other inflammatory diseases or autoimmune disorders^[68]. From the results, it has been highly predicted that serum CHI3L1 levels seem to be a potential and promising biomarker for malignant tumors.

The expression of CHI3L1 is relatively restricted to a limited number of cell types: it is totally absent in monocytes^[69] and marginally expressed in monocyte-derived dendritic cells^[70], but is strongly induced during the late stages of human macrophage differentiation^[43]. Rehli *et al*^[43] clearly demonstrated that promoter

Table 2 Expression of CHI3L1 in solid tumors

Solid tumors	Location	Ref.
Glioma, Oligodendroglioma, glioblastoma	Brain	[74,123-132]
Squamous cell carcinoma of the head and neck	Head and neck	[18,22,62]
Lung cancer (small cell carcinoma)	Lung	[133,134]
Breast cancer	Breast	[4,8,21,55,57,62,67,68,75,132-141]
Colorectal cancer	Colon	[20,132]
Kidney tumor	Kidney	[132,142,143]
Hepatocellular carcinoma	Liver	[21,66]
Ovarian tumor, endometrial cancer	Ovary	[55-61,133,138,139]
Primary prostate cancer	Prostate	[23,63,144]
Metastatic prostate cancer		
Papilloma thyroid carcinoma, thyroid tumor	Thyroid	[136,145]
Extracellular myxoid-chondrosarcoma	Bone	[146]
Multiple myeloma	Bone marrow	[147,148]
Hodgkin's lymphoma	Lymph node	[65]
Malignant melanoma	Melanocyte	[18,64]
Myxoid liposarcoma	Fat cells	[146]

elements (in particular, the proximal -377 base pairs of the CHI3L1 promoter region) control the expression of CHI3L1 in the macrophage used. CHI3L1 is also expressed in neutrophils^[71], chondrocytes^[3], fibroblast-like synoviocytes^[72], vascular smooth muscle cells^[5], vascular endothelial cells^[73], ductal epithelial cells^[67], hepatic stellate cells^[18], and colonic epithelial cells^[10]. In physiological concentrations CHI3L1 tends to promote proliferation of these cell types. CHI3L1 is a transmembrane protein whose extracellular domain can undergo cleavage^[39]. The cleaved components bind to putative receptor(s) on the cell surface or soluble receptor(s), but these receptors have not been identified yet^[18,40]. Some reports suggest that CHI3L1 can play an important role in tumor invasion. Nigro *et al*^[74] showed that immortalized human astrocytes stably transfected with CHI3L1 increased invasion across a chemotactic gradient *in vitro*. Roslind *et al*^[75] demonstrated that metastatic tumor cells in blood vessels, lymph nodes and skin displayed the same pattern of CHI3L1 as primary breast cancer cells by immunohistochemical analysis: normal epithelial cells display the widespread strong dot-like staining in the whole cytoplasm, while the dot-like staining is localized in the restricted area of cytoplasm in malignant tumor cells. Indeed, CHI3L1 is strongly expressed in the invasive front of lobular carcinoma which is adjacent to normal epithelial cells. These studies suggest that CHI3L1 may assist the migration of malignant cells and support metastasis of cancer cells by promoting the malignant transformation of adjacent normal epithelial cells.

A POSSIBLE BIOLOGICAL ROLE OF CHI3L1 IN ONCOGENIC PROGRAMMING PROCESS

It has been predicted that CHI3L1 can have a growth

Table 3 Inflammation-associated carcinogenic change

Inflammatory disorder	Carcinogenic formation	Ref.
Human papillomavirus infection	Cervical carcinoma	[149-152]
Crohn's disease, ulcerative colitis	Colorectal carcinoma	[153-159]
Chronic cholecystitis	Gall bladder carcinoma	[160-162]
Hepatitis B, C infection	Hepatocellular carcinoma	[163-167]
Asbestosis, asthma, <i>C. pneumoniae</i> infection, chronic obstructive lung disease, middle lobe syndrome, silicosis	Lung carcinoma	[168-174]
Pelvic inflammatory disease	Ovarian carcinoma	[175-177]
Chronic pancreatitis	Pancreatic carcinoma	[178-183]
<i>H pylori</i> infected gastritis	Gastric carcinoma, lymphoma	[184-186]
Chronic cystitis, schistosomiasis	Bladder carcinoma	[187-190]
Primary sclerosing cholangitis	Cholangio carcinoma, colorectal carcinoma, liver carcinoma, pancreatic carcinoma	[191]

stimulating effect since a family of CHI3L molecules in the fruit fly *Drosophila melanogaster* regulates the growth of imaginal disc cells^[76]. 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^[73]. 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^[20]. 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^[79]. Inflammation was recently recognized as an important

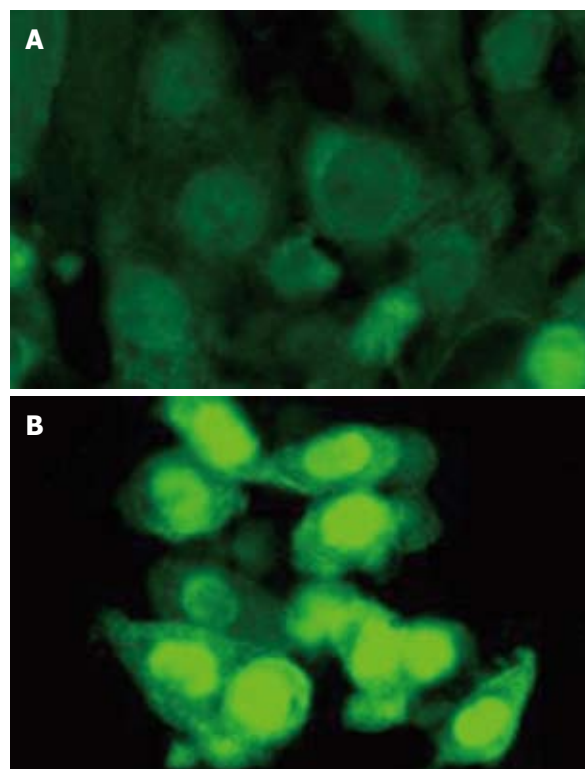


Figure 1 Activation of β -catenin in colonic epithelial cells by purified Chitinase 3-like-1 (CHI3L1). SW480 human colon cancer cells were cultured without (A) or with purified human CHI3L1 protein (50 ng/mL) for 24 h (B), and cells were stained with mouse anti-human β -catenin monoclonal antibody followed by FITC-horse anti-mouse IgG staining. Purified CHI3L1 significantly stimulates the nuclear translocation of β -catenin in SW480 cells. Original magnification, objective 40 \times .

factor in the pathogenesis of malignant tumors^[80] 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^[81]. Therefore, CHI3L1 is strongly associated with cell survival and cell migration during the drastic tissue remodeling processes by interacting with extracellular matrix components^[39,40].

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-nuclear 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

activation of gp130/STAT3 transcription factor regulates cell cycle progression as well as survival of enterocytes during chronic colitis-associated tumor promotion^[85-88]. 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 AMCCase, 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.

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