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MINIREVIEWS

Olfactomedin-4 in digestive diseases: A mini-review

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Abstract

Olfactomedin-4 (OLFM4, GW112, hGC-1) is a glycoprotein belonging to the olfactomedin family. The expression of OLFM4 is strong in the small intestine, colon and prostate, and moderate in the stomach and bone marrow. Previous studies have revealed that OLFM4 is closely associated with many digestive diseases. Up-regulation of OLFM4 has been detected in the *Helicobacter pylori* (*H. pylori*)-infected gastric mucosa, inflammatory bowel disease tissue and gastrointestinal malignancies, including gastric cancer, colorectal cancer, pancreatic cancer and gallbladder cancer. Down-regulation of OLFM4 has also been detected in some cases, such as in poorly differentiated, advanced-stage and metastatic tumors. Studies using OLFM4-deficient mouse models have revealed that OLFM4 acts as a negative regulator of *H. pylori*-specific immune responses and plays an important role in mucosal defense in inflammatory bowel disease. Patients with OLFM4-positive gastric cancer or colorectal cancer have a better survival rate than OLFM4-negative patients. However, the prognosis is worse in pancreatic cancer patients with high levels of expression of OLFM4. The NF-κB, Notch and Wnt signaling pathways are involved in the regulation of OLFM4 expression in digestive diseases, and its role in pathogenesis is associated with anti-inflammation, apoptosis, cell adhesion and proliferation. OLFM4 may serve as a potential specific diagnostic marker and a therapeutic target in digestive diseases. Further studies are required to explore the clinical value of OLFM4.

Key words: Olfactomedin-4; Inflammation; Cancer; *Helicobacter pylori* infection

Core tip: This review is based on the currently available literature about olfactomedin-4 (OLFM4) and is intended to reveal the link between OLFM4 and digestive diseases, including *Helicobacter pylori* infection, inflammatory bowel disease and gastrointestinal malignancies. The data on the expression, function and regulatory pathways of OLFM4 in digestive diseases are summarized. The potential clinical value of OLFM4 in digestive diseases is also discussed.

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INTRODUCTION

Olfactomedin-4 (OLFM4, also called GW112 or hGC-1) is a 72-kDa glycoprotein belonging to the olfactomedin family and is characterized by the presence of an olfactomedin domain with approximately 250 amino acids, which is located in the C-terminal region[1]. OLFM4 was initially cloned from human hematopoietic myeloid cells treated with granulocyte colony-stimulating factor[1]. The *OLFM4* gene, located on chromosome 13q14.3, encodes a 510-amino acid N-linked glycoprotein with the olfactomedin domain[1,2]. OLMF4 can be expressed in the membrane, cytoplasm, nucleus, mitochondria and mature neutrophil granules[1,3-5]. OLFM4 is strongly expressed in the small intestine, colon and prostate, moderately expressed in the stomach and bone marrow, and weakly expressed or not expressed in other tissues[1].

Compared with that in normal tissues, aberrant expression of *OLFM4* has been detected in many pathological tissues, such as the gastric mucosa infected with *Helicobacter pylori* (*H. pylori*)[6,7], inflamed intestinal tissue in inflammatory bowel disease[8,9] and many types of gastrointestinal malignancies[10-14] (Figure 1). The primary function of *OLFM4* in gastrointestinal malignancies is associated with its role as an antiapoptotic factor that promotes the tumor growth[4]. In addition, *OLFM4* down-regulates innate immunity against *H. pylori* infection[7] and affects the anti-inflammatory function in inflammatory bowel disease[15]. In this review, we summarize the data on the expression, function and regulatory pathways of OLFM4 in digestive diseases.

OLFM4 IN *H. PYLORI* INFECTION

Expression

H. pylori infection is a well-recognized risk factor for gastric diseases as well as extra-gastric diseases[16-18]. The host immune response plays a key role in the course and outcome of *H. pylori* infection[19,20]. The innate immune system serves as the first line of defense against *H. pylori* infection[21]. An adaptive immune response to *H. pylori* is also elicited in nearly all *H. pylori*-infected individuals[22]. OLFM4 is a novel glycoprotein that negatively regulates the host defense system against bacterial infection[23].

An early microarray study found that OLFM4 expression is significantly up-regulated in the gastric mucosa of *H. pylori*-infected patients compared with that in uninfected controls[6]. OLFM4 expression was also found to be significantly up-regulated in the gastric mucosa of *H. pylori*-infected mice. However, further study is warranted to determine whether eradication of *H. pylori* leads to the normalization of OLFM4 levels. The expression of OLFM4 is up-regulated in neutrophils, macrophages and epithelial cells after *H. pylori* infection, which suggests that overexpression of OLFM4 upon *H. pylori* infection is due to its direct action on epithelial cells as well as to activation of neutrophil and macrophage infiltration[7], thus suggesting a potential role for OLFM4 in the host immune response against *H. pylori* infection.

Function

The exact function of OLFM4 in *H. pylori* infection has been demonstrated by generating an OLFM4-deficient mouse model. Colonization of *H. pylori* in the gastric mucosa is significantly reduced after knocking out the *OLFM4* gene, as compared with that in wild-type mice[7]. In addition, in response to *H. pylori* infection, infiltration of inflammatory cells was significantly enhanced, the production of proinflammatory cytokines and chemokines was increased, and the bacterial load was reduced in OLFM4-deficient mice[7]. Therefore, OLFM4 acts as a negative regulator of the *H. pylori*-specific immune responses[7].

Regulation

OLFM4 is a target gene of the NF-κB pathway and expression of the *OLFM4* gene can be regulated by the transcription factor NF-κB[7,24]. The regulation is achieved by binding of NF-κB to the 5′-upstream region of the *OLFM4* gene[24]. Moreover, OLFM4 exerts a negative feedback effect on the NF-κB pathway[7].

Mouse experiments have revealed that *H. pylori* infection up-regulates the OLFM4 expression in an NF-κB-dependent manner, and then, due to the negative feedback effect of OLFM4, the *H. pylori*-induced NF-κB activation is down-regulated[7]. Furthermore, OLFM4 inhibits the nucleotide oligomerization domain (NOD)-1/2-mediated NF-κB activation and subsequent cytokine and chemokine production through direct association with NOD1 and NOD2[7]. The reduced cytokine and chemokine production results in a weak inflammatory response and a high level of colonization of *H. pylori* in the gastric mucosa[7].

Experiments in a MyD88 and OLFM4 double-

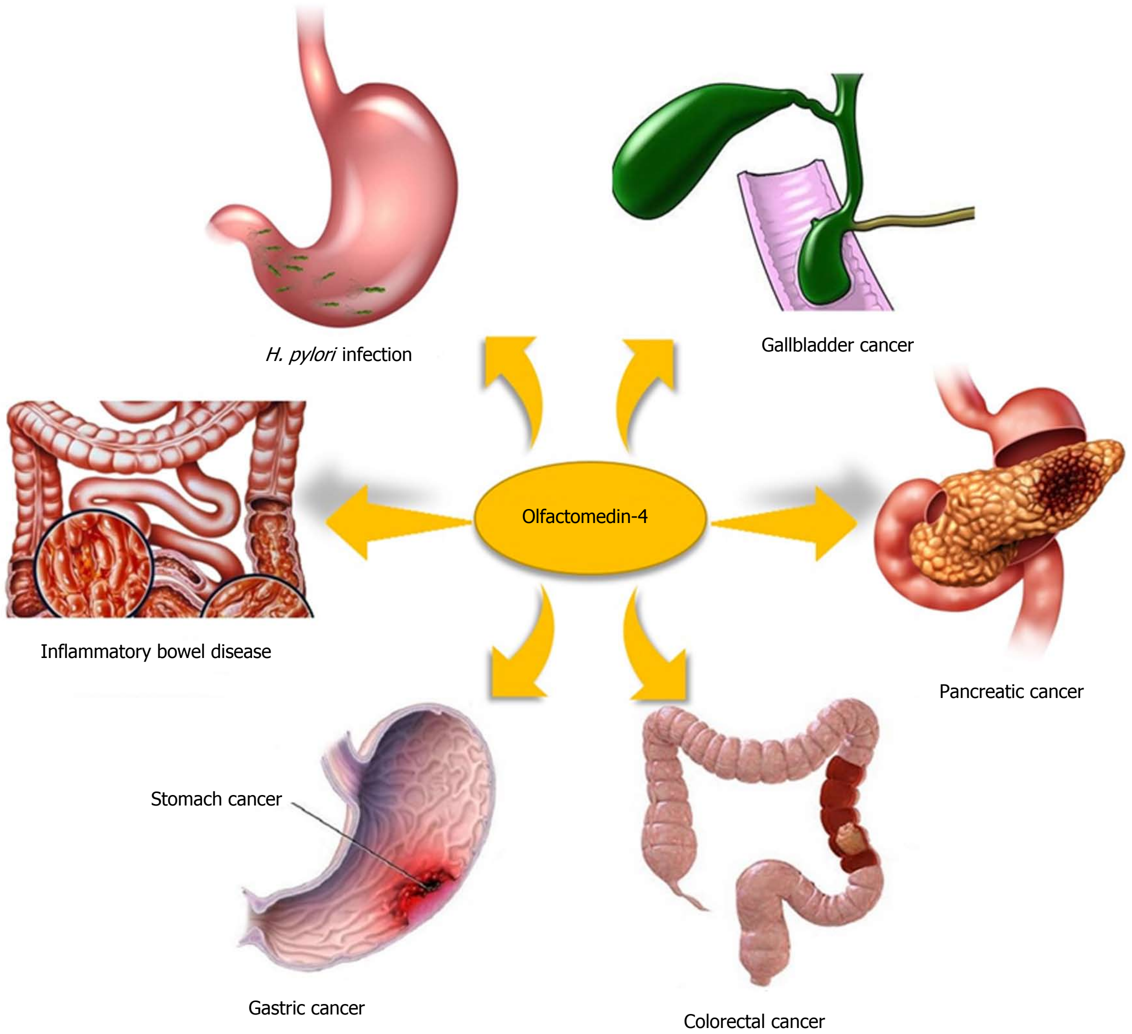

Figure 1 Relationship between olfactomedin-4 and digestive diseases. Olfactomedin-4 is related to *Helicobacter pylori* infection, inflammatory bowel disease and gastrointestinal malignancies, including gastric cancer, colorectal cancer, pancreatic cancer and gallbladder cancer.

knockout mouse model have demonstrated that the *H. pylori* colonization level in the model is similar to that in wild-type mice[25]. Even though the immune and inflammatory responses are enhanced compared with those in wild-type mice, infiltration of inflammatory cells in the gastric mucosa of double-knockout mice is lower than that in OLFM4 knockout mice[25]. Additionally, knocking out OLFM4 significantly up-regulates the MyD88 expression. It has been shown that deletion of OLFM4 indirectly increases the MyD88 expression by enhancing NOD2 expression, whereas the deficiency of MyD88 leads to a loss of the feedback inhibition of the NF-κB pathway and of the resulting response[25,26].

OLFM4 IN INFLAMMATORY BOWEL DISEASE

Expression

OLFM4 is a robust marker for murine intestinal stem cells as well as human intestinal stem cells[27]. Both OLFM4 mRNA and protein expression levels are significantly up-regulated in the intestinal epithelium in Crohn's disease and ulcerative colitis[8,9]. Compared with that in inflamed tissue from Crohn's disease patients, the OLFM4 expression is more obviously increased in inflamed tissue from patients with active ulcerative colitis[8,9]. Moreover, in active ulcerative colitis, the expression of OLFM4 expands to the surface of epithelial cells as well as to the crypt lumen, and OLFM4 seems to be secreted into the mucus[8,9]. In contrast, the *OLFM4* gene expression is almost absent in luminal surface cells and mesenchymal cells and is confined to the lower third of the crypt in normal tissues[8,9].

Function

OLFM4 plays an important role in the mucosal defense of the stomach and colon[9]. Experiments using OLFM4-deficient mice have revealed severe inflammation and proliferation in intestinal crypts in small intestines[15]. Serious inflammation and mucosa damage have also been found in the colon of OLFM4-deficient mice[15].

The anti-inflammatory function of OLFM4 in inflammatory bowel disease is consistent with that in the stomach. The function against inflammatory bowel disease may be related to the tissue-specific human beta-defensins (HBD)1, HBD2 and HBD3. As mucus components with different electric charges, OLFM4 and HBD1–3 can interact, and the binding ability of OLFM4 was ranked, from high to low, as HBD3 > HBD2 > HBD1[9]. Furthermore, OLFM4 binding leads to a decrease in the antimicrobial activities of HBD1-3[9].

Regulation

OLFM4 is a target gene for the Notch signaling pathway, which regulates intestinal cell proliferation and differentiation[28]. The expression of OLFM4 increases after activation of Notch signaling[28]. Conversely, the expression of OLFM4 rapidly decreases after treatment with the Notch blocker dibenzazepine[9,28]. Researchers have found that after mesenchymal stem cell transplantation, the expression of OLFM4 is down-regulated, while that of Atoh1 is up-regulated[29]. This result suggests that the suppression of Notch signaling leads to decreased OLFM4 expression.

Although some studies have shown that cell incubation with TNF-α alone does not influence the OLFM4 expression, some other studies have found that TNF-α and components of the Notch pathways synergistically up-regulate the OLFM4 expression[9,30,31]. TNF-α is one of the most important proinflammatory cytokines promoting inflammatory bowel disease[30]. Microarray analysis has revealed that up to 21 genes are involved in the synergistic up-regulation of TNF-α and the Notch intracellular domain[30]. Further studies have suggested a markedly increased expression of OLFM4, reaching up to a 2500-fold increase in LS174T cells, when overexpression of Notch intracellular domain-1 (NICD1) or hairy and enhancer of split-1 (HES1) is combined with TNF-α stimulation[30,31]. Such a synergistic effect is mediated through transcriptional regulation, which is dependent on a proximal NF-κB binding site[31].

OLFM4 IN GASTROINTESTINAL CANCER

Increased *OLFM4* expression has been reported in some gastrointestinal cancers, such as gastric cancer[10,11,32,33], pancreatic cancer[12] and early-stage colon cancer[13,14]. In addition, the expression of OLFM4 is correlated with the histological type of cancer, differentiation, lymphatic metastasis and prognosis[10,11,34]. Furthermore, OLFM4 is relevant to many cellular processes, including cell adhesion, apoptosis and proliferation[2,11,35]. Therefore, OLFM4 may serve as a candidate biomarker for these gastrointestinal cancers[36]. Here, we briefly summarize the recent advances in the expression, function and regulation of OLFM4 in gastrointestinal cancers.

Gastric cancer

Up-regulated OLFM4 expression is a frequent event in the gastric mucosa in gastric cancer[10,11,32,33]. Highly expressed OLFM4 is found in intestinal-type adenocarcinoma, while OLFM4 expression does not occur in diffuse-type adenocarcinoma[10]. Moreover, enhanced expression of OLFM4 occurs in well- or moderately differentiated and early-stage adenocarcinomas, and the expression is remarkably decreased or even lost in poorly differentiated and advanced-stage gastric cancer[10]. Furthermore, the OLFM4 expression is higher in patients without lymphatic metastasis than in those with lymphatic invasion[11,37]. OFLM4 expression is also related to the prognosis. OLFM4-positive gastric cancer patients have a better survival rate than do OLFM4-negative patients[34,37]. Using serum OLFM4 alone or in combination with human regenerating protein IV as biomarkers for gastric cancer patients is more sensitive than using CA199[32]. Down-regulation of OLFM4 suppresses the tumor proliferation, migration and invasion of gastric cancer cells *in vitro*[33,38].

The *OLFM4* gene was found to be up-regulated *via* the NF-κB signaling pathway and to exert an antiapoptotic effect in gastric cancer[39]. The anti-apoptotic effect caused by OLFM4 can be induced by reducing H_2O_2 or TNF-α[38]. Moreover, the antiapoptotic factor OLFM4 is a direct target of miR-486, which is a frequently lost microRNA (miRNA) in gastric cancer patients and may act as a tumor suppressor miRNA in gastric cancer[40]. miR-486 directly targets and inhibits OLFM4 and thereby induces antioncogenic effects against gastric cancer[40].

Colorectal cancer

OLFM4 is enriched in human colon crypts, although it is not expressed in the murine colon[15,27,41,42]. It has been universally accepted that OLFM4 is a useful marker of intestinal stem cells (ISCs) in humans, similar to LGR5, which is a confirmed ISC marker[27,43,44]. Up-regulation of OLFM4 is detected more frequently in highly differentiated and early-stage colon cancers than in the normal colon mucosa, whereas it is often down-regulated or not expressed in poorly differentiated, late tumor-node-metastasis stage, and metastatic cancers[35]. OLFM4-positive colorectal cancer patients have a better survival rate than do OLFM4-negative patients[45]. In addition, precancerous colorectal lesions also show aberrant OLFM4 expression. For example, OLFM4 is expressed in a diffuse manner in traditional serrated adenomas, while other ISC markers such as LGR5 and ASCL2 are localized as in normal tissue[44]. OLFM4 silencing enhances the proliferation in intestinal crypts and inflammation initiated by azoxymethane/dextran sodium sulfate[15]. Moreover, systemic OLFM4 deletion promotes colon tumorigenesis, which may be associated with the loss of mucosal neutrophils[15].

There is an intimate connection between OLFM4, Wnt/β-catenin signaling, crypt biology[15,46-48] and colon cancer[27,49,50]. OLFM4 is a target gene that acts as a negative regulator of the Wnt/β-catenin signaling pathway and inhibits colon cancer progression by down-regulating the Wnt signaling pathway[15].

Pancreatic cancer

OLFM4 mRNA is expressed at higher levels in pancreatic cancer tissues than in noncancerous pancreatic tissue samples[12]. In addition, OLFM4 was found to be

Table 1 Effects of olfactomedin-4 in digestive diseases

Disease	Expression	Function	Regulation
H. pylori infection	Up-regulated in the *H. pylori*–infected gastric mucosa	Negative regulator of *H. pylori*-specific immune responses	NF-κB, NOD-1/2, MyD88
Inflammatory bowel disease	Up-regulated in the intestinal epithelium in Crohn's disease and ulcerative colitis	Mucosal defense, anti-inflammatory effects	Notch, TNF-α
Gastrointestinal malignancies	Up-regulated in well/moderately differentiated, early-stage gastrointestinal malignancies without lymphatic metastasis	Biomarker, candidate therapeutic target	NF-κB, TNF-α, miR-486, Wnt/β-catenin

H. pylori: *Helicobacter pylori*.

significantly over-expressed in peripheral blood mononuclear cells in pancreatic cancer patients compared with its expression in a control group[51]. Furthermore, OLFM4 has also been detected in pancreatic juice and ascites[52]. Pancreatic cancer may occur in a background of chronic pancreatitis. Whether OLFM4 is associated with chronic pancreatitis or acute pancreatitis flares is worth further investigation. In the PANC-1 cell line, OLFM4 is especially increased during the early S phase of the cell cycle and promotes proliferation by supporting the S to G2/M phase transition[12]. OLFM4 binds to the apoptosis-promoting factor GRIM-19 to induce antiapoptosis[4]. Pancreatic cancer patients with high levels of OLFM4 expression have a worse prognosis[53].

Gallbladder cancer

Similar to the above findings, expression of the *OLFM4* gene has been found to be increased in gallbladder cancer tissues[54]. In addition, the expression level of OLFM4 is significantly related to the age of gallbladder cancer patients[54]. However, further studies are needed to clarify the precise role of OLFM4 in gallbladder cancer.

CONCLUSION

Since the initial discovery of OLFM4, researchers have explored many aspects of OLFM4, including its aberrant expression, biological functions and related mechanisms (Table 1). The expression of OLFM4 has been relatively well studied in normal tissues as well as in numerous diseases. The anti-inflammatory and antiapoptotic roles of OLFM4 are generally accepted. However, the exact mechanism for its effects in gastrointestinal diseases remains to be determined. Moreover, the clinical applications of OLFM4 as a specific detection marker or a therapeutic target need to be defined in the future.

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