Upregulation of SLC11A2 in gastric cancer patients with Helicobacter pylori infection

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Abstract

Introduction: H. pylori infection has a strong association with prevalence of iron deficiency and gastric cancer (GC). Cancer cells reprogram the iron metabolism in order to provide required iron. H. pylori is also need iron for its own growth and reproduction. SLC11A2 encodes a member of the solute carrier family 11 protein family which involved in transportation of divalent metals and iron absorption. We evaluated the relative expression of SLC11A2 in patients with GC and its relation to H. pylori infection and pathological characteristics of tumor.

Materials and methods: Forty-five patients with GC were involved in this research of whom 24 patients have been infected with H. pylori. Relative expression of SLC11A2 gene was estimated by quantitative real-time PCR. The relationship of SLC11A2 expression change with Pathological characteristics such as size and grade of tumor cells, lympho-vascular and perineural invasion and clinical stage of disease were evaluated in both infected and uninfected patients.

Results: SLC11A2 relative expression was significantly higher (P =0.026) in GC patients infected with H. pylori (11.33 ± 5.22) in comparison to those without infection (2.56 ± 0.65). Although it was not statistically significant, the expression of SLC11A2 in all participants was higher at higher stages (III &IV) of disease (9.84 ± 4.35) in comparison to those with lower stages (2.54 ± 0.75). However, among the patients infected with H. pylori, SLC11A2 expression was significantly (P= 0.027) upregulated in the higher stages of disease (16 ± 7.6) compare to the lower stages (1.8 ± 1.06).

Conclusion: SLC11A2 is probably a target gene for H. pylori in order to supply its need to iron. The relative expression changes of SLC11A2 in GC patients were associated with the infection of H. pylori, and pattern of its association with the prognosis of the disease changes in the presence and absence of infection with H. pylori.

Keywords: SLC11A2, Gastric cancer, H. pylori

Introduction

Iron plays an important role in cell crucial functions and metabolic pathways like heme synthesis and electron transport chain (1). Iron, as a cofactor is necessary in many redox reactions such as energy production, and neurotransmitter maintenance (2). A large

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number of proteins are involved in iron uptake, transport, storage, detoxification and utilization. Iron dysregulation can lead to the promotion and progression of many diseases, like iron deficiency (ID), iron overload, and other disorders (3-5). Iron contributes to cancer through different mechanisms like the production of reactive oxygen species (ROS) and induction of transcription factors in response to oxidative stress (6, 7). Iron also stimulates oncogenic pathways (8), and affects the process involved in DNA synthesis (9), DNA repair (10), and the cell cycle (11, 12).

An increasing number of genes mutants involved in iron metabolism have been reported to cause diseases, such as HFE gene in hereditary hemocromatosis (13, 14). A transmembrane transporter protein, solute carrier family 11, member 2 (SLC11A2) have physiological importance in bringing iron into cells, because Iron cannot pass through cellular membranes unassisted. The SLC11A2 gene encodes a divalent metal transporter (DMT1) which carries iron, manganese, cobalt, nickel, cadmium, lead, copper, and zinc. DMT1 participates in cellular iron absorption at the luminal surface of the duodenum as well as in other areas of the body (15).

SLC11A2 may participate in transfer of iron to the cytoplasm in transferrin cycle endosomes in erythroid precursors (16). It has been involved in materno-fetal iron transfer (17, 18) and non–transferrin-bound iron uptake (19). Other iron uptake activities have been described in cultured cells, although their physiological significances are unknown (20-22).

Recently the biological association of iron to gastric cancer has attracted a considerable attention. The role of H. Pylori in gastric inflammation and its clinical outcomes including peptic ulcers, atrophic gastritis and gastric cancer is well recognized (23, 24). H. pylori infection has a strong association with prevalence of iron deficiency (25). Iron is an essential element for proliferation and growth of cells and its metabolism is well-regulated in body (26, 27). Iron metabolism, include iron achievement, diffusion, storage and regulation is reprogramed in cancer cells in order to ensure tumor survival.

With regard to the role of SLC11A2 in iron uptake by cell and the importance of iron metabolism in tumor cell's growth and proliferation, in this study the relative expression changes of SLC11A2 in tumor cells in comparison with normal adjacent tissue in GC patients were investigated and the relation of SLC11A2 expression with presence of H. pylori infection was evaluated.

Materials and methods

Patients and specimens

Biological materials were provided by Iran National Tumor Bank which was founded by Cancer Institute of Tehran University of Medical Sciences, in this study. Forty-five patients with gastric cancer who underwent surgery in Cancer Institute of Iran were selected for this study. None of the selected patients have received any chemotherapy or radiotherapy prior to surgery. Patients were diagnosed with GC based on histopathological examination. The pathological data of patients were recorded according to the pathology report include the histology, tumor size, grade, lymphovascular invasion and clinical TNM (Tumor, Node, and Metastasis) staging. Subjects with chronic or acute inflammatory diseases or any other synchronize primary tumor were also excluded from the study. All samples were prepared with full observation of preparation and preservation processes of standard protocols base on ethical permission and obtaining written informed consent from all donors.

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Helicobacter pylori infection confirmation

Infection with H. pylori was confirmed by histology examination of specimens. Infection was determined by Giemsa staining of paraffin fixed formalin embedded sections and identified as rods on the surface of the epithelium, microscopically. Twenty-four out of 45 cases were identified as H. pylori positive infection.

RNA extraction and real-time quantitative (RT-PCR)

Primer sequences for SLC11A2 were designed and synthesized by Sinaclon Company, Iran. Forward and reverse primers for SLC11A2 were 5'-TCTGGAGATCATGGGGAGTC-3' and 5'-TCCTCCTCAGGAATGGAGAT-3' respectively. β2M was designated as housekeeping gene that Forward and reverse primers for β2M were 5'-GATCAAGATCATTGCTCCTCCTG-3' and 5'-CTAGAAGCATTTGCGGTGGAC-3' respectively.
RNA was extracted using GeneAll® Hybrid-RTM kit (GeneAll Biotechnology, Seoul, Korea) according to the manufacturer's instructions. After normalization of all extracted RNA to 1µg, RNA was reverse transcribed into single strand cDNA using Takara kit (Takara, Japan) fallowing the protocols. The quantity and purity of extracted RNA was analyzed by Nano-Drop instrument (Technologies, ND-2000). The product was used for quantitative RT-PCR using syber green /ROX (Takara, Japan) real time PCR master mix based on the protocol of *Exicycler*™ 96 Real-Time Quantitative Thermal Block from Bioneer (Exicycler 96, Bioneer Company, Korea). The amplification protocol comprised of 1 cycle at 95 °C for 4 min followed by 40 cycles at 95 °C for 15 s, 60 °C for 30 s. The cycle of threshold (CT) was determined by Bioneer software. The relative expression of the studied genes to the housekeeping gene was calculated by measuring the delta threshold cycle value (ΔCT) for each sample. Delta delta cycle value (ΔΔCT) was then calculated from the difference between ΔCT of tumor sample and normal adjacent tissue. The fold change in expression was then calculated by $2^{-\Delta\Delta CT}$ formula.

Statistical analysis

Statistical analyses were performed by SPSS software version 23. Data were expressed as mean ± SD. Statistical differences of SLC11A2 expression level between tumor samples and normal adjacent tissue was determined by two tailed Mann–Whitney U test. A P less than 0.05 was considered statistically significant.

Results

Nine female and 36 male patients with GC average age of 61.2 ± 1.8 years old were involved in this study. Table 1 shows the demographic and pathology characteristics of all participants.
Comparison of SLC11A2 mean expression change between tumor samples and normal adjacent tissues is shown in figure 1. SLC11A2 expression was significantly ($P < 0.05$) upregulated (3.3 ± 0.6) in tumor samples when compare with normal adjacent tissue. Figure 2 shows the comparison of SLC11A2 relative expression in GC patients with H. pylori infection in comparison with those who not infected. As indicated, SLC11A2 mean fold change in GC patients with H. pylori infection was significantly higher than non-infected GC patients (11.3 ± 5.2 folds versus 2.5 ± 0.6 folds, $P = 0.026$).
Relationship between SLC11A2 relative expression with clinic-pathological factors include age, gender, site of primary, family history of cancer, tumor size, necrosis, lympho-vascular and perineural invasion, grade and stage of disease were investigated in this study.

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Table 1. The demographic and pathology characteristics of participants.

Characteristics	N (%)	SLC11A2	P-value
Age			
<60	22 (48.9)	2.99 ± 0.74	0.147
≥60	23 (51.1)	11.31 ± 5.45	
Gender			
Female	9 (20)	1.48 ± 0.42	0.050*
Male	36 (80)	8.68 ± 3.53	
Site of primary			
Cardia	8 (17.8)	3.61 ±1.43	0.543
Antrum	8 (17.8)	2.3 ± 0.65	
Body	29 (64.4)	9.61 ± 4.36	
Tumor size			
<5 cm	21 (46.7)	6.48 ± 4.16	0.897
≥5 cm	24 (53.3)	7.59 ± 3.98	
Grade			
Low grade (I & II)	28 (62.2)	6.41 ± 3.43	0.713
High grade (III & IV)	17 (37.8)	8.61 ± 5.11	
Stage			
Low stage (I & II)	16 (35.6)	2.54 ± 0.75	0.224
High stage (III & IV)	29 (64.4)	9.84 ± 4.35	
Necrosis			
Present	12 (26.7)	9.57 ± 7.51	0.699
Absent	33(73.3)	6.40 ± 2.84	
Lymphatic invasion			
Present	26 (57.8)	7.56 ± 3.58	0.899
Absent	19 (42.2)	6.80 ± 4.74	
Vascular invasion			
Present	29 (64.4)	6.97 ± 3.23	0.907
Absent	16 (35.6)	7.74 ± 5.63	
Perineural invasion			
Present	25 (55.6)	7.47 ± 3.72	0.847
Absent	20 (44.4)	6.62 ± 4.51	
Family History			
Present	22 (48.9)	8.38 ± 4.32	0.703
Absent	23 (51.1)	6.16 ± 3.81	
H pylori infection			
Positive	24 (53.3)	11.33 ± 5.22	0.026*
Negative	21 (46.7)	2.56 ± 0.65	

Data are expressed as mean ± SD. P <0.05 is considered significant.

As indicated in Table 1, there was a significant increase (P =0.05) in SLC11A2 relative expression in male GC patients (8.6 ± 3.5) in comparison to female patients (1.4 ± 0.4). SLC11A2 was more upregulated in tumors located in the body of stomach in comparison with cardia or antrum. Comparison of SLC11A2 mean expression change between tumor samples and normal adjacent tissues in all patients is shown in Figure 1. Expression level of SLC11A2 in tumors was over than threefold (3.3 ± 0.6) when compared with normal tissue. Upregulation of SLC11A2 was more significant in tumors of patients which infected with H. pylori in comparison to not infected patients (11.33 ± 5.22 to 2.56 ± 0.65, P =0.026) (Figure 2). The relationship between SLC11A2 mean fold change and grade of tumor in GC patients is seen in Figure 3. Expression levels of SLC11A2 had an increased in higher grade of tumor, although it was not significant. Figures 4 and 5 indicate the relation of SLC11A2 expression with the stages of disease. The expression of SLC11A2 in all participants

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was higher at higher stages (III & IV) of disease (9.8 ± 4.3) in comparison to those with lower stages (2.5 ± 0.7), although it was not statistically significant. However, this difference in expression was significant when was evaluated among the patients infected with H. pylori, (16 ± 7.6 to 1.8 ± 1.06, P =0.02).

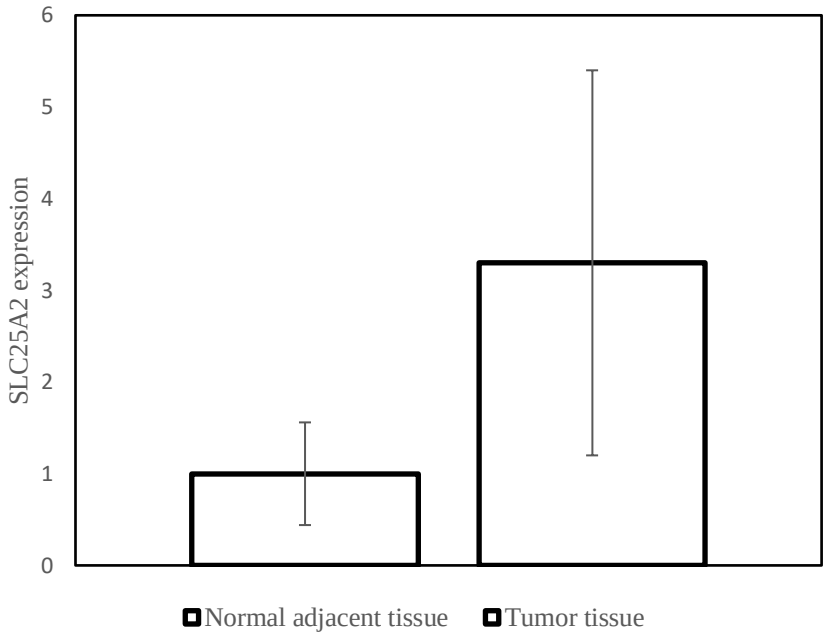


Figure 1. Comparison of SLC11A2 mean expression change between tumor samples and normal adjacent tissues. Data are expressed as mean ± SD.

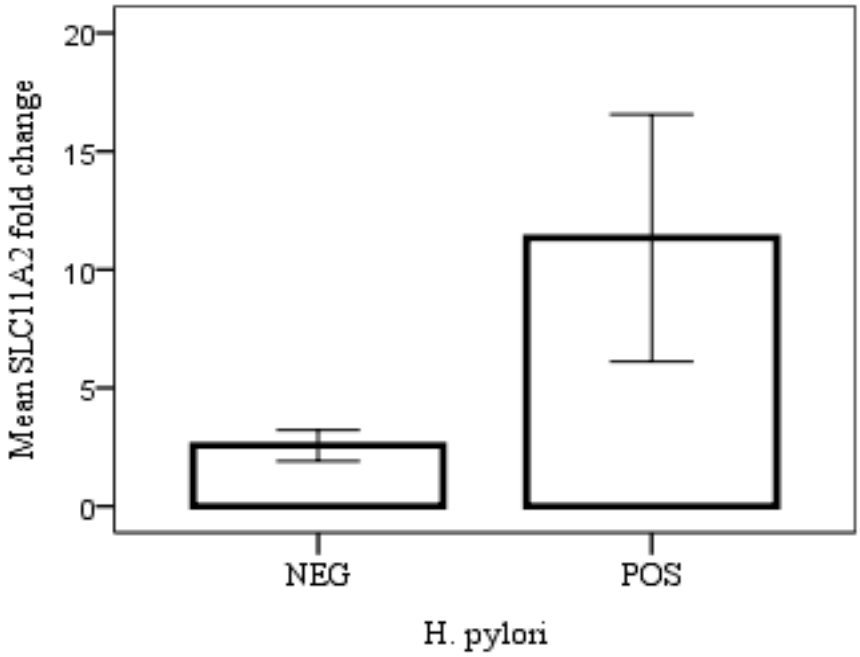


Figure 2. Comparison of SLC11A2 mean fold change between H. pylori positive and H. pylori negative GC patients. Data are expressed as mean ± SD.

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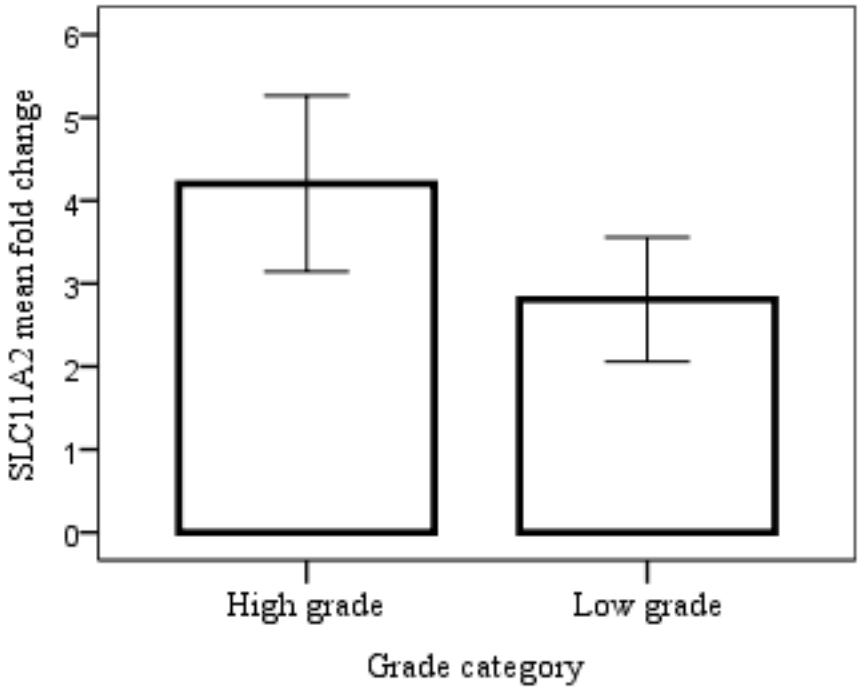


Figure 3. Evaluation of the relationship between SLC11A2 mean fold change and grade of tumor in GC patients. Data are expressed as mean ± SD.

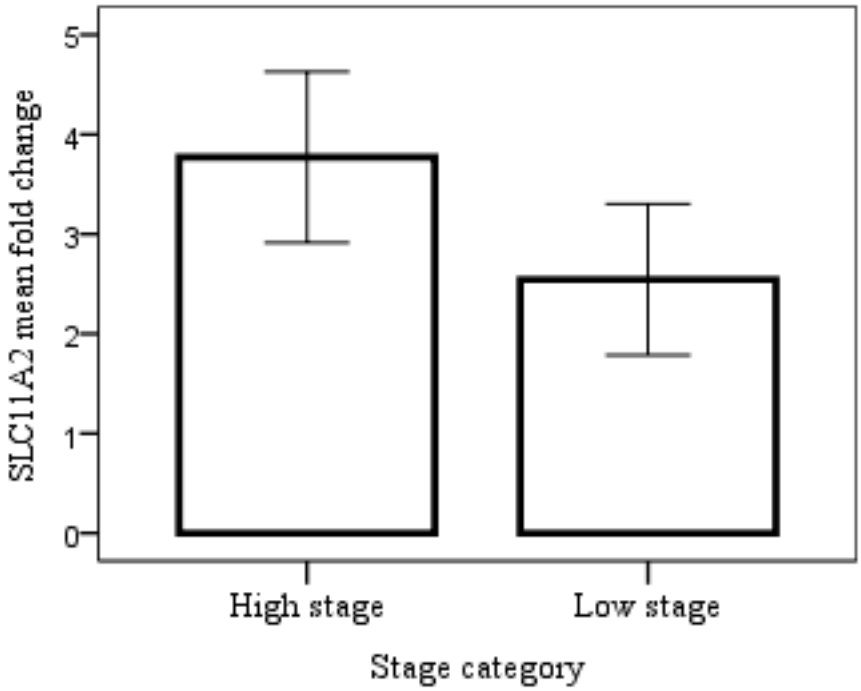


Figure 4. Evaluation of the relationship between SLC11A2 mean fold change and stage of disease in all GC patients. Data are expressed as mean ± SD.

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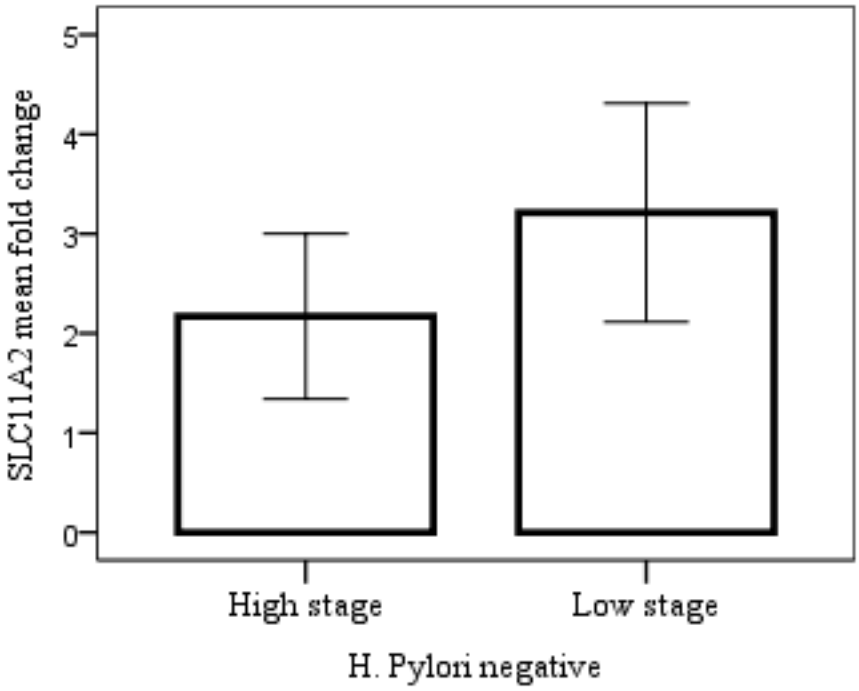


Figure 5. Evaluation of the relationship between SLC11A2 mean fold change and stage of disease in GC patients without H. Pylori infection. Data are expressed as mean ± SD.

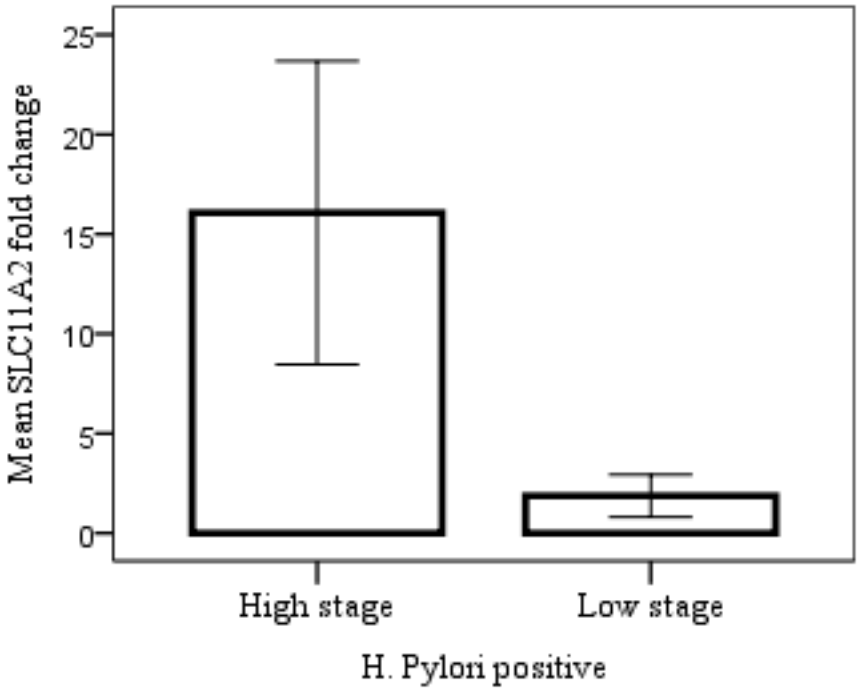


Figure 6. Evaluation of the relationship between SLC11A2 mean fold change and stage of disease in GC patients with H. Pylori infection. Data are expressed as mean ± SD.

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Discussion

In this study we investigated the SLC11A2 relative expression in GC patients and evaluated the relation of its expression change with clinic-pathological characteristics of disease in presence and absence of H. pylori infection. Our data indicated a significant increase in SLC11A2 relative expression in H. pylori positive GC patients in comparison to those without infection.

H. pylori is considered as an important risk factor in GC (28) and induce its carcinogenicity by up regulation of cag A and cag T4SS expression, especially in iron low condition (29). H. pylori modulates iron hemostasis in the host cells and promotes oncogenic responses through disturbing multiple hosts signaling pathways (30). Regulation of iron homeostasis is very important in bacterial pathogens, so iron metabolism pathways may be one of the possible targets for H. pylori in order to ensure bacteria survival. A large proportion of the genes are involved in iron uptake and storage whose expression changed dramatically at the Log-Stat of bacterial growth (31). Changes in SLC11A2 expression in GC patients with H. pylori infection are probably in line with the objectives of bacteria to control the metabolism of iron.

Tumor cells in comparison with normal cells need more iron for facilitates cell proliferation and growth (32). Elevated levels of SLC11A2 expression in GC can increase intracellular iron uptake and make it available to fast growing tumor cells. In this study, higher expression levels of SLC11A2 in stages III and IV of disease specially in tumors infected with H. pylori were seen.

Previously a number of alterations in the expression of genes involved in iron metabolism have been reported in tumor cells (33). TFR1 expression was shown to be up-regulated in tumor cells with a high rate of proliferation (34-36). Treatment with anti-TfR1 monoclonal antibodies inhibits hematopoietic tumor cell growth *in vitro* (36). However tumor cells like human melanoma and hepatoma cells use non-receptor mediated pinocytosis to uptake iron without binding of Trf to TfR1 (37). IRP–IRE mechanism regulates the expression of TfR1 based on intracellular iron levels (38). Animal studies carrying a G185R missense mutation in Slc11a2 suggested that the protein was important for both intestinal iron absorption and erythroid iron utilization (39). Although symptoms of gastric cancer appear late and gastric cancer is still recognized as a deadly disease, Therefore, there is a need to inform the public about the signs and symptoms of the disease and to emphasize early referral to the physician as well as the necessary measures for timely diagnosis and initiation of treatment. Identification of molecular and genetic markers will improve the diagnosis and treatment of patients. The results of this study may indicate the diagnostic value of this gene expression in patients with gastric cancer and Helicobacter pylori infection. Perhaps by increasing the sample size, more complete information about the expression status of this gene and its association with the factors under study can be obtained and this gene can be used as a biomarker in the diagnosis and prognosis of gastric cancer. It is noteworthy that this study is a preliminary investigation of this claim and further studies and analyzes should be carried out to confirm it.

Conclusion

SLC11A2 expression levels were upregulated in GC tumor cells especially in patients infected with H. pylori. SLC11A2 probably is a target gene for H. pylori in order to supply its need to iron. Over expression of SLC11A2 may be a useful diagnostic and prognostic biomarker in GC.

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Conflict of interests

The authors declare that they have no financial conflict of interest.

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