

## RESEARCH ARTICLE

# IL-17A Levels in the Sera of Patients with Gastric Cancer Show Limited Elevation

Zahra Malek-Hosseini<sup>1</sup>, Marziye Taherinejad<sup>2</sup>, Mahyar Malekzadeh<sup>2</sup>, Abbas Ghaderi<sup>1,2</sup>, Mehrnoosh Doroudchi<sup>1,2\*</sup>

### Abstract

**Background:** Inflammation plays a major role in the development and progression of gastric and other gastrointestinal tumors. The IL-17 family of cytokines has been under investigation as targets of immunotherapy. **Materials and Methods:** We investigated the levels of IL-17A inflammatory cytokine in the sera of 57 patients with gastric cancer (GC) and 90 healthy age/sex matched controls using ELISA methods. **Results:** In only 5 (8.8%) of the patients' sera was IL-17A detectable. No IL-17A was apparent in the sera of healthy controls. The maximum concentration of IL-17A in patients was 7.004 pg/ml. Vascular and lymphatic invasions were only seen in one of the 5 positive cases. Although all of them were in the age group >60 years, no correlation was seen between age and IL-17A level. These results are somewhat different from our findings for colorectal cancer (CRC) in the same population. **Conclusions:** It is possible that the inflammopathology of CRC and GC are rather different, at least in Fars, a southern province of Iran.

**Keywords:** Gastric cancer - IL-17A - Serum - ELISA - Iran

*Asian Pac J Cancer Prev*, 16 (16), 7149-7153

### Introduction

Gastric cancer (GC) is the fourth most common malignancy and the second most common cause of cancer death worldwide. It is more common in men and in developing countries, and almost two-thirds of the new cases per year occur in developing countries (Parkin et al., 2005; Tsugane and Sasazuki, 2007). There is a wide variation in the incidence of gastric cancer in different geographical regions.

In Iran, Ardabil, a northwestern province, has the highest incidence of gastric cancer followed by Mazandaran and Golestan provinces in the north (Malekzadeh et al., 2009). Semnan and Tehran metropolitan area also have high rates of gastric cancer in both men and women. In contrast to the northern areas, gastric cancer in the south-central province, Kerman, has a lower incidence (Malekzadeh et al., 2009). In a 6-year study published in 2013, it was reported that gastric cancer is the second common cancer in males and the sixth in females in Shiraz, Fars province in the south (Mehrabani et al., 2013). Moreover, Hassanzade et al. reported that stomach and colorectal cancers to cause higher mortality rates than the average national cancer mortality in the south of Iran (Hassanzade et al., 2011).

The three most common primary malignant gastric neoplasms are adenocarcinoma (95%), lymphoma (4%), and malignant gastrointestinal stromal tumors (GIST) (1%) (Rokkappanavar K. Kumar, 2013). Gastric cancer

is a multi-factorial disease and develops as a result of continuous cell damage caused by life-long exposure to different carcinogens (Malekzadeh et al., 2009). Chronic atrophic gastritis, *Helicobacter pylori* infection, smoking, heavy alcohol use, and several dietary factors (high intake of salted, smoked or pickled foods, and low intake of fruits and vegetables) have been linked to increased risks of gastric cancer (Layke and Lopez, 2004). In addition, gastric cancer is regulated by different host factors such as cytokines which can modulate tumor growth and microenvironment by mediating interactions between cancer cells and infiltrating inflammatory cells (Landskron et al., 2014).

One of the important inflammatory cytokines is Interleukin-17 (IL-17) which together with Interleukin-23 (IL-23) are suggested to play a role in the *H. pylori*-associated pathology of gastric cancer (Caruso et al., 2007; Liu et al., 2014a). IL-17, also known as IL-17A, is the prototypic member of the IL-17 family composed of six cytokines, IL-17A-F. Among all the members, the two cytokines IL-17A and IL-17F share the strongest sequence homology (Jin and Dong, 2013). IL-17 family cytokines mediate their biological functions via binding to surface receptors on target cells. The biologic activity of IL-17 is dependent on a complex composed of IL-17RA and IL-17RC by which the signals are transduced to the cell (Toy et al., 2006).

The main IL-17 producing cells are Th17 cells,

<sup>1</sup>Department of Immunology, School of Medicine, <sup>2</sup>Shiraz Institute for Cancer Research, Shiraz University of Medical Sciences, Shiraz, Iran \*For correspondence: mdroroud@sums.ac.ir

however, other CD4+ and CD8+ T cells,  $\gamma\delta$ -T cells, natural killer (NK) T cells, neutrophils and eosinophils produce IL-17, as well (Meng et al., 2012). The expansion and survival of Th17 cells require other inflammatory cytokines such as IL-6, TGF- $\beta$  and IL-23 (Caruso et al., 2007; Wang et al., 2009). TLR and Nod2 signaling can increase MCP-1 and RANTES expression on tumor cells and tumor-derived fibroblasts that can promote the recruitment of Th17 cells to the tumor site (Su et al., 2010).

Several studies strongly suggest that Th17 cytokine responses are protective against most extracellular bacteria *Staphylococcus aureus*, *Citrobacter rodentium* (e.g. *S. aureus*, *C. rodentium* and *Klebsiella pneumoniae*) (Jin and Dong, 2013). However, in some cases (e.g. *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis*), Th17 response and IL-17 contribute to the pathology of infection (Tesmer et al., 2008). *H. pylori*, a gram negative bacterium, is a major element in the induction of gastritis and its progression to gastric cancer. In this case, too, persistent inflammation induced in part by IL-17 may contribute to gastric mucosal pathology, thereby increasing the risk of gastric cancer.

*H. pylori* infection causes a marked infiltration of the gastric mucosa with neutrophils, macrophages, and lymphocytes. Antigens released by *H. pylori* can stimulate endothelial cells, macrophages and epithelial cells to make large amounts of chemokines, such as IL-8 that promotes migration of neutrophils into the gastric mucosa. Both macrophages and epithelial cells also synthesize neutrophil-recruiting chemokines in response to lamina propria mononuclear cell (LPMC)-derived molecules. IL-17A, a key regulator of neutrophil chemotaxis, is produced in excess in *H. pylori*-infected stomach. On the other hand, IL-17A stimulates the production of IL-1, IL-6, and TNF- $\alpha$  and induces fibroblasts to make matrix metalloproteinases (MMPs) contributing to the mucosal damage. IL-23/IL-17 pathway is not only an important driving force of *H. pylori* mediated gastric inflammation, but also, IL-23A is shown to be secreted from GC cells and macrophages in correlation with tumor volume and *H. pylori* infection (Caruso et al., 2007; Liu et al., 2014). IL-23A had no direct effect on the proliferation of cancer cells, and affected the tumor microenvironment by increasing secretion of IL-17A. Interestingly, serum IL-23A levels were the indicator of poor prognosis in GC patients.

The serum concentration of IL-23A and/or IL-17A are reported to increase in *H. pylori*+ patients with gastric cancer (Liu et al., 2014a) and other gastroduodenal diseases (Matveeva and Mosina, 2013). It is noteworthy that CD8+ T cells are also a main population of cells that contribute to IL-17 production. It has been shown that increased serum IL-17 concentration in GC patients shows a significant positive correlation with the frequency of CD8+ T cells producing IL-17 (Tc17) (Saito et al., 2015). Increased levels of IL-17 in the sera and tumoral tissues of patients with gastric cancer are already demonstrated in other geographical areas of Asia (Meng et al., 2012). Also a study performed in Kerman province of Iran showed that the mean IL-17 serum levels in patients with duodenal ulcer were significantly higher than that of asymptomatic and healthy uninfected control individuals (Jafarzadeh et

al., 2009). To our best of knowledge, there is no report on the serum IL-17A levels in Fars province of Iran with a relatively high rate of gastric cancer. In the previous studies in this same area, we have observed a higher level of IL-17A in the sera of patients with colorectal (Nemati et al., 2015) as well as glioma, bladder and ovarian cancers (Doroudchi et al., 2013a; Doroudchi et al., 2013b; Malekzadeh et al., 2013). Therefore, in a preliminary study to evaluate the possible increase of IL-17A in the sera of GC patients in our area, we measured the IL-17A and its association with some clinicopathological factors in a group of Iranian patients with gastric cancer residing in Fars region.

## Materials and Methods

### Patients and samples

This is a case-control study on patients with gastric cancer who referred to the hospitals of Shiraz University of Medical Sciences. None of the patients received chemotherapy, or surgical treatment before the study. The diagnosis of disease was confirmed by histopathologic examination. Clinical data of patients and controls were acquired from the clinical records and by a questionnaire. Patients with a history of cancer or the simultaneous existence of other cancer(s), autoimmunity, and known family history of inflammatory or autoimmune diseases in first-degree relatives were excluded. All patients and healthy individuals signed informed consent to participate. Healthy individuals had no personal sign of diseases at the time of sampling and no family history of cancer, inflammatory or autoimmunity and were chosen from among the samples in the bio-bank of Shiraz Institute for Cancer Research, Shiraz, Iran. All protocols were approved by the Ethics Committee of Shiraz University of Medical Sciences. Serum samples were obtained from 57 patients ( $60.40 \pm 16.12$  yrs, range = 19-85 yrs) and 90 age- and sex-matched healthy controls ( $59.12 \pm 15.20$  yrs, range = 21-86 yrs) and stored at  $-70^{\circ}\text{C}$  until analyzed.

### Enzyme-linked immunosorbent assay (ELISA) for IL-17A

The level of IL-17A in sera was determined using a commercial ELISA kit (eBioscience, Austria), according to the protocols described by the manufacturer. Briefly, 100 microliter ( $\mu\text{L}$ ) of 1:2 diluted sera, standards and controls were added to wells pre-coated with monoclonal antibody to human IL-17A. Then 50  $\mu\text{L}$  of Biotin-conjugated anti-human IL-17A monoclonal antibody was added and the plates were incubated at room temperature for 2 hours with constant shaking. After four washing steps, the plates were incubated with 100  $\mu\text{L}$  of Streptavidin-HRP (enzyme conjugate) for 1 hour at room temperature with constant shaking, followed by adding 100  $\mu\text{L}$  of TMB (3,3',5,5'-Tetramethyl benzidine) solution to each well for 10 min in the dark. The reaction was stopped by the addition of 100  $\mu\text{L}$  of stop solution and the absorbance was measured using an ELISA reader (Anthos, Austria) at 450 nm with reference wavelength 620 nm. IL-17A concentrations in the samples were calculated through plotting a standard curve of known concentrations of the standards against optical density (OD). The sensitivity of

ELISA was 0.5 pg/mL according to the manufacturer. All values above this level were considered positive.

### Statistical analysis

All data analysis was performed by using SPSS 15.0 for windows (version 11.5, SPSS Inc., Chicago, IL., USA). Student t-test was used to compare the serum levels of IL-17A between patients and healthy control group. Comparison between serum levels of IL-17A in patients group based on depth of invasion, stage of tumor, etc. was performed by Mann-Whitney test. Chi-square test was used to evaluate the correlation between stage and age, gender and depth of invasion and between histological grade and lymphatic and vascular invasion. P values of  $\leq 0.05$  were considered statistically significant.

## Results

Sera of 57 patients with gastric cancer and 90 healthy age- and sex-matched were assessed for IL-17A levels. The characteristics of patients are shown in Table 1. Totally, 94% of patients had adenocarcinoma type of

**Table 1. The Demographic Data of Patients and Pathologic Characteristics of Gastric Tumors**

Variables	Gastric cancer n (%)*
age (Mean $\pm$ SD)	60.47 $\pm$ 16.12 yrs
Sex, no. (%)	
Male	44 (77.19)
Female	13 (22.81)
Tumor stage, no. (%)	
Stage I/II	15 (26.31)
Stage III/IV	27 (47.36)
Tumor grade, no. (%)	
Well differentiated	20 (35.1)
Moderately or Poorly differentiated	31 (54.38)
Tumor type, no. (%)	
Adenocarcinoma	54 (94.73)
Other	3 (5.27)
Vascular invasion, no. (%)	
Absent	29 (50.87)
Present	13 (22.8)
Lymphatic invasion, no. (%)	
Absent	18 (31.57)
Present	14 (24.56)

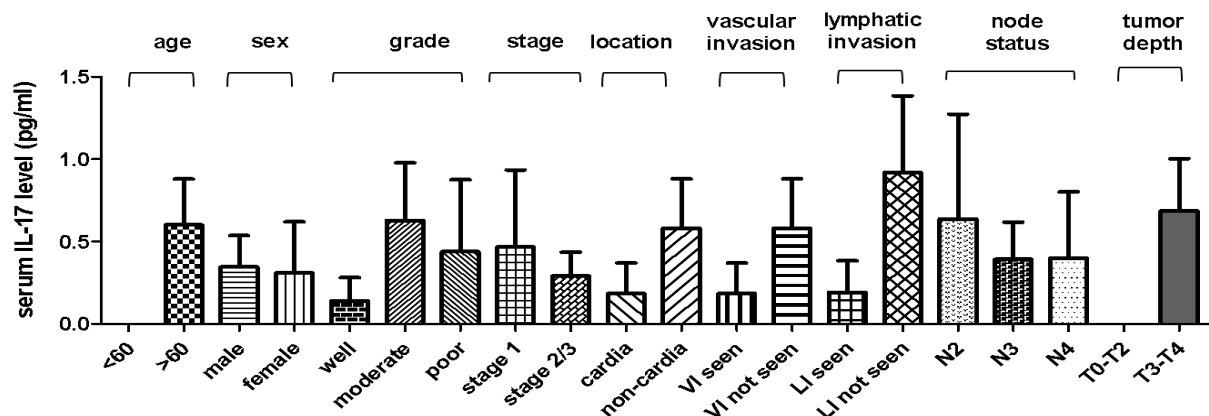
GC tumor. There was no difference between the serum concentration of IL-17A in patients and control group using student t-test.

The mean concentrations of IL-17A in the patients based on their clinicopathological grouping are shown in figure 1. While moderate/poor differentiation, low stage, high tumor depth and lack of vascular and lymph node invasion were likely to be seen in connection with higher serum IL-17A, none of the differences reached the statistical significance probably due to the limited number of positive cases.

Among the 57 patients of gastric cancer, sera of only 5 patients were positive for IL-17A. No IL-17A was detectable (above the sensitivity of the assay) in the rest of the patients and also in control individuals. The maximum concentration of IL-17A in patients was 7.004 pg/ml. Vascular and lymphatic invasions were only seen in one case but not in the other 4 cases. Although all of the 5 positive patients were in the age group of  $>60$  years, no correlation was seen between age and IL-17A level. In relation to the tumor grade, one of the 5 positive patients had well differentiated, three had moderately differentiated and the other one patient had poorly differentiated tumor grades.

## Discussion

In the current study we found only 5 (8.8%) of 57 patients with gastric cancer had elevated IL-17A in their sera. This percentage is somewhat different to our previous finding in patients with colorectal cancer in the same area of Iran (Nemati et al., 2015). In colorectal cancer, mostly adenocarcinomas, we found a high percentage of IL-17A elevation in patients, which correlated with the tumor size. In several studies in East Asia, the high expression and release of IL-17A in the sera of gastric cancer patients has been reported (Liu et al., 2014a; Liu et al., 2014b; Saito et al., 2015). In accordance with these findings, other reports from East Asia suggest a correlation between different polymorphisms of IL-17A and gastric cancer as well (Ren et al., 2014; Wang et al., 2014; Yu et al., 2014). While we did not analyze the polymorphisms of IL-17A in the current study, our previous report on the genotypes and allelic frequencies of this gene in colorectal cancer showed distinction with other populations of the region (Omrane



**Figure 1. Mean Serum Concentrations of IL-17A Based on Patients Criteria**

et al., 2014; Nemati et al., 2015). Therefore, it would be interesting to see how different the role of inflammatory cytokines of IL-17 family and their genes would be in the populations of East and West Asia.

The dual role of IL-17 in the tumor associated inflammation and anti-tumor immunity has been suggested in previous studies. It is demonstrated that IL-17 can promote tumor growth, angiogenesis and metastasis, and in the others its anti-tumor activity is highlighted. In an experiment on a murine fibrosarcoma cell line and animal models of fibrosarcoma, it has been shown that IL-17 stimulates production of proangiogenic factors like VEGF, MIP-2, PGE1, PGE2, and NO in fibroblasts and promotes angiogenesis via stimulation of vascular endothelial migration (Numasaki et al., 2003). Another study showed that IL-17 promoted colorectal cancer (CRC) (Wu et al., 2013). Moreover, a Foxp3+ IL-17+ T cell population in CRC tumor tissue is suggested to suppress the tumor-specific CD8+ T cells and thereby attenuate the antitumor response (Ma and Dong, 2011). It has been shown that increased density of intratumoral IL-17 producing cells promotes hepatocellular tumor progression through enhancing angiogenesis (Zhang et al., 2009). Similarly, Th17 cells in pancreatic tumor tissues, and Th17 cells, IL-17 and IL-23 in peripheral blood of patients were associated with tumor stage, suggesting the involvement of Th17 and IL-17 in the invasion and metastasis of pancreatic cancer (He et al., 2011).

Although IL-17 seems to be a potential tumor-promoting cytokine, a great number of reports have described antitumor effects of IL-17. Th17 cells were found to be more effective than Th1 cells in eliminating large established melanoma tumors (Murugaiyan and Saha, 2009). In addition, IL-17 has been shown to inhibit the growth of hematopoietic tumors such as mastocytoma and plasmacytoma by enhancing CTL activity through IL-17- induced IL-6 and IL-12 production by macrophages (Benchetrit et al., 2002). Kryczek et al. showed that tumor growth and lung metastasis were enhanced in IL-17-deficient mice (Kryczek et al., 2009). The antitumor role of IL-17 in esophageal squamous cell carcinoma was demonstrated by the positive correlation of IL-17+ tumor infiltrating lymphocytes (TILs) with the frequency of CD8+ CTLs and CD57 + NK cells and its association with better overall survival (Lv et al., 2011).

Since production of IL-17A by the immune cells is dependent on other inflammatory cytokines (Caruso et al., 2007; Wang et al., 2009) and the tumor itself is also a cytokine-rich milieu, a myriad of interactions between different cytokines exists in the tumor microenvironment. Other members of IL-17 family may also affect the functional significance of IL-17A in different tumors, where there is still some debate on its dual role in tumor progression or tumor suppression. It is shown that mutations in the oncogenes, which appear during colon cancer progression, can affect IL-17 expression (Petanidis et al., 2013). In addition, the genetic makeup of the host as well as the temporal changes in the tumor behavior in adaptation to the immune response can modify the expression levels of the tumor-associated cytokines which affect their functional relevance (Ma et al., 2015). No need

to emphasize that both elements along with the tumor type are determinants of tumor microenvironment and cytokine milieu in which a specific cytokine, e.g. IL-17, is having an impact. Therefore, it is not surprising to see dissimilar associations in different tumor types or different populations (2002) Coupland et al., 2012; Oluwasola, 2014; Yan et al., 2014). Several previous studies have shown differential distribution of gastric cancer as well as *H. pylori* infection in different ethnicities around the world and in the countries. In this sense a lower prevalence of *H. pylori* in Shiraz, Fars province compared to the northern Golestan province of Iran is noteworthy (Ghasemi-Kebria et al., 2013; Niknam et al., 2014). We also observed that all of the 5 positive patients were in the age group of >60 years. One might argue that the elevation of IL-17A in these patients is related to age and *H. pylori* infection. While the *H. pylori* infection of patients was not addressed in our study, previous reports from Iran show that *H. pylori* infection is quite prevalent in all age groups of rather healthy individuals in this country (Eshraghian, 2014).

In conclusion, we suggest that IL-17A may have limited importance in the pathogenesis of gastric cancer in the Fars province of Iran but to confirm this, a much larger study which also evaluates genes and proteins of other IL-17 family members and the rate of *H. pylori* infection in the patients is necessary.

## Acknowledgements

This work was performed as part of M. Taherinejad dissertation as a requirement for graduation as a general practitioner from Shiraz Medical School (Shiraz, Iran). This project was financially supported by a grant (89-01-2309) from Shiraz University of Medical Sciences and was performed in Shiraz Institute for Cancer Research, Shiraz, Iran. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

## References

- Benchetrit F, Ciree A, Vives V, et al (2002). Interleukin-17 inhibits tumor cell growth by means of a T-cell-dependent mechanism. *Blood*, **99**, 2114-21.
- Cancer incidence in five continents (2002). Volume VIII. *IARC Sci Publ*, 1-781.
- Caruso R, Pallone F, Monteleone G (2007). Emerging role of IL-23/IL-17 axis in H pylori-associated pathology. *World J Gastroenterol*, **13**, 5547-51.
- Coupland VH, Lagergren J, Konfortion J, et al (2012). Ethnicity in relation to incidence of oesophageal and gastric cancer in England. *Br J Cancer*, **107**, 1908-14.
- Doroudchi M, Pishhe ZG, Malekzadeh M, et al (2013a). Elevated serum IL-17A but not IL-6 in glioma versus meningioma and schwannoma. *Asian Pac J Cancer Prev*, **14**, 5225-30.
- Doroudchi M, Saidi M, Malekzadeh M, et al (2013b). Elevated IL-17A levels in early stages of bladder cancer regardless of smoking status. *Future Oncol*, **9**, 295-304.
- Eshraghian A (2014). Epidemiology of *Helicobacter pylori* infection among the healthy population in Iran and countries

- of the Eastern Mediterranean Region: a systematic review of prevalence and risk factors. *World J Gastroenterol*, **20**, 17618-25.
- Ghasemi-Kebria F, Ghaemi E, Azadfar S, et al (2013). Epidemiology of *Helicobacter pylori* infection among Iranian children. *Arab J Gastroenterol*, **14**, 4.
- Hassanzade J, Molavi e vardanjan iH, Farahmand M, et al (2011). Incidence and mortality rate of common gastrointestinal cancers in south of iran, a population based study. *Iran J Cancer Prev*, **4**, 7.
- He S, Fei M, Wu Y, et al (2011). Distribution and clinical significance of Th17 cells in the tumor microenvironment and peripheral blood of pancreatic cancer patients. *Int J Mol Sci*, **12**, 7424-37.
- Jafarzadeh A, Mirzaee V, Ahmad-Beygi H, et al (2009). Association of the CagA status of *Helicobacter pylori* and serum levels of interleukin (IL)-17 and IL-23 in duodenal ulcer patients. *J Dig Dis*, **10**, 107-12.
- Jin W, Dong C (2013). IL-17 cytokines in immunity and inflammation. *Emerging Microbes and Infections*, **2**, 1-5.
- Kryczek I, Wei S, Szeliga W, et al (2009). Endogenous IL-17 contributes to reduced tumor growth and metastasis. *Blood*, **114**, 357-9.
- Landskron G, De la Fuente M, Thuwajit P, et al (2014). Chronic inflammation and cytokines in the tumor microenvironment. *J Immunol Res*, **2014**, 149185.
- Layke JC, Lopez PP (2004). Gastric cancer: diagnosis and treatment options. *Am Fam Physician*, **69**, 1133-40.
- Liu C, Zhang Y, Zhan J, et al (2014a). Interleukin-23A is associated with tumor growth in *Helicobacter-pylori*-related human gastric cancer. *Cancer Cell Int*, **14**, 104.
- Liu X, Jin H, Zhang G, et al (2014b). Intratumor IL-17-positive mast cells are the major source of the IL-17 that is predictive of survival in gastric cancer patients. *PLoS One*, **9**, 106834.
- Lv L, Pan K, Li XD, et al (2011). The accumulation and prognosis value of tumor infiltrating IL-17 producing cells in esophageal squamous cell carcinoma. *PLoS One*, **6**, 18219.
- Ma C, Dong X (2011). Colorectal cancer-derived Foxp3(+) IL-17(+) T cells suppress tumour-specific CD8+ T cells. *Scand J Immunol*, **74**, 47-51.
- Ma M, Jin GJ, Yun K, et al (2015). Correlation of IL-1F genetic polymorphisms with the risk of colorectal cancer among Chinese populations. *Tumour Biol*, **36**, 807-14.
- Malekzadeh M, Dehaghani AS, Ghaderi A, et al (2013). IL-17A is elevated in sera of patients with poorly differentiated ovarian papillary serous cystadenocarcinoma. *Cancer Biomark*, **13**, 417-25.
- Malekzadeh R, Derakhshan MH, Malekzadeh Z (2009). Gastric cancer in Iran: epidemiology and risk factors. *Arch Iran Med*, **12**, 576-83.
- Matveeva LV, Mosina LM (2013). The changes in serum concentrations of interleukin-17 in diseases gastroduodenal zone. *Eksp Klin Gastroenterol*, **8**, 24-7.
- Mehrabani D, Hosseini SV, Rezaianzadeh A, et al (2013). Prevalence of stomach cancer in Shiraz, Southern Iran. *J Res Med Sci*, **18**, 335-7.
- Meng XY, Zhou CH, Ma J, et al (2012). Expression of interleukin-17 and its clinical significance in gastric cancer patients. *Med Oncol*, **29**, 3024-8.
- Murugaiyan G, Saha B (2009). Protumor vs antitumor functions of IL-17. *J Immunol*, **183**, 4169-75.
- Nemati K, Golmoghaddam H, Hosseini SV, et al (2015). Interleukin-17FT7488 allele is associated with a decreased risk of colorectal cancer and tumor progression. *Gene*, **561**, 88-94.
- Niknam R, Seddigh M, Fattahi MR, et al (2014). Prevalence of *Helicobacter pylori* in Patients With Dyspepsia. *Jundishapur J Microbiol*, **7**, 12676.
- Numasaki M, Fukushi J, Ono M, et al (2003). Interleukin-17 promotes angiogenesis and tumor growth. *Blood*, **101**, 2620-7.
- Oluwasola AO (2014). Genetic determinants and clinicopathological outcomes of *Helicobacter pylori* infection. *Ann Ib Postgrad Med*, **12**, 22-30.
- Omrane I, Marrakchi R, Baroudi O, et al (2014). Significant association between interleukin-17A polymorphism and colorectal cancer. *Tumour Biol*, **35**, 6627-32.
- Parkin DM, Bray F, Ferlay J, et al (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, **55**, 74-108.
- Petanidis S, Anastakis D, Argyraki M, et al (2013). Differential expression of IL-17, 22 and 23 in the progression of colorectal cancer in patients with K-ras mutation: Ras signal inhibition and crosstalk with GM-CSF and IFN-gamma. *PLoS One*, **8**, 73616.
- Ren Z, Li M, Liu R, et al (2014). Interleukin 17A rs3819024 A>G polymorphism is associated with an increased risk of gastric cardia adenocarcinoma in a Chinese population. *Biomarkers*, **19**, 411-6.
- Rokkappanavar K, Kumar SSR, Esaki M, Shankar, E Ganapathy, Abdul S Ebrahim, Shukkur M Farooq (2013). Gastric Carcinoma- New Insights into Current Management 271-93, edited by Daniela Lazăr, ISBN 978-953-51-0914-3, InTech, January 1, 2013
- Saito H, Yamada Y, Takaya S, et al (2015). Clinical relevance of the number of interleukin-17-producing CD8+ T cells in patients with gastric cancer. *Surg Today*.
- Su X, Ye J, Hsueh EC, et al (2010). Tumor microenvironments direct the recruitment and expansion of human Th17 cells. *J Immunol*, **184**, 1630-41.
- Tesmer LA, Lundy SK, Sarkar S, et al (2008). Th17 cells in human disease. *Immunol Rev*, **223**, 87-113.
- Toy D, Kugler D, Wolfson M, et al (2006). Cutting edge: interleukin 17 signals through a heteromeric receptor complex. *J Immunol*, **177**, 36-9.
- Tsugane S, Sasazuki S (2007). Diet and the risk of gastric cancer: review of epidemiological evidence. *Gastric Cancer*, **10**, 75-83.
- Wang L, Yi T, Kortylewski M, et al (2009). IL-17 can promote tumor growth through an IL-6-Stat3 signaling pathway. *J Exp Med*, **206**, 1457-64.
- Wang N, Yang J, Lu J, et al (2014). IL-17 gene polymorphism is associated with susceptibility to gastric cancer. *Tumour Biol*, **35**, 10025-30.
- Wu D, Wu P, Huang Q, et al (2013). Interleukin-17: a promoter in colorectal cancer progression. *Clin Dev Immunol*, **2013**, 436307.
- Yan S, Li B, Bai ZZ, et al (2014). Clinical epidemiology of gastric cancer in Hehuang valley of China: a 10-year epidemiological study of gastric cancer. *World J Gastroenterol*, **20**, 10486-94.
- Yu H, Sun S, Liu F, et al (2014). Meta-analysis of associations between interleukin-17 gene polymorphisms and risk of gastric cancer. *Asian Pac J Cancer Prev*, **15**, 8709-13.
- Zhang JP, Yan J, Xu J, et al (2009). Increased intratumoral IL-17-producing cells correlate with poor survival in hepatocellular carcinoma patients. *J Hepatol*, **5**, 980-9.