Annals of Medicine and Surgery 9 (2016) 1–5

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.annalsjournal.com

Review

Interleukin (*IL*)-4 -590C>T polymorphism is not associated with the susceptibility of gastric cancer: An updated meta-analysis

Tie Wang [a], Lining Tian [b], Meizhuo Gao [c], Hongjiang Song [a], Yuzhe Wei [a], Yingwei Xue [a, *]

[a] Department of Gastrointestinal Surgery, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang Province, China
[b] Department of Medical Education, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, China
[c] Department of General Surgery, The Forth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang Province, China

HIGHLIGHTS

- Gastric cancer (GC) is a malignant disease with a poor outcome in which genetic background plays roles during pathogenesis.
- The polymorphism of *IL-4 -590C>T* may not be related with the susceptibility of GC.
- Further investigations on the relationship of *IL-4 -590C>T* and subtypes of GC are needed.

ARTICLE INFO

Article history:
Received 7 May 2016
Received in revised form
12 May 2016
Accepted 12 May 2016

Keywords:
Gastric cancer
Polymorphism
Interleukin-4
Susceptibility
Meta-analysis

ABSTRACT

Gastric cancer (GC) is a common cancer affecting patients around the world. The pathogenesis of gastric cancer has not been understood completely. Genetic mutations and the inflammation induced by *Helicobacter pylori* (HP) seem to play important roles. The cytokine Interleukin-4 (IL-4) has effects in inflammation, allergies and cancer including GC. The association of *IL-4 -590 C>T* polymorphism and gastric cancer has been studied in different populations with inconsistent results. Here, we report this meta-analysis showing that the polymorphism of *IL-4 -590C>T* might not be associated with the GC susceptibility in both Asian and Caucasian populations.

Contents

* Corresponding author.
E-mail address: medwang@163.com (Y. Xue).

http://dx.doi.org/10.1016/j.amsu.2016.05.011

1. Introduction

Gastric cancer (GC) is one of the most common cancers worldwide, and the third leading cause of cancer related death [1,2]. Although the incidences and mortality of GC are declining, countries in Eastern Asia including China, Korea and Japan still have the highest prevalence in the world, where half of new cases occur.

The outcome of GC is poor since almost half of surgical patients with GC will suffer recurrence even after adjuvant therapies [3]. The reason for this unfavorable outcome is the etiology of GC is complex and remains incompletely understood. The pathogenesis of GC is a multifactorial and multistep process among which chronic *Helicobacter pylori* (HP) infection, environmental toxins, personal diet habits and genetics background [4] are the key components. Chronic and persistent presence of HP infection, which induces long-term inflammation in the stomach, plays an important role in several sequential steps of the pathogenesis of GC [5].

Since GC is a pathogen-induced carcinoma, the inflammatory microenvironment of GC has gained great interest from researchers. Among interleukins (IL) which mediate many effects in inflammation, IL-4 is the major IL for T helper (Th)-2 mediated inflammation and important in maintaining Th1/Th2 balance [6]. IL-4 has the potential to activate alternatively activated macrophages (AAMs) and inhibits the secretion of proinflammatory cytokines including IL-1, IL-6, interferon-γ and tumor necrosis factor-α to promote tumor cells [6]. IL-4 has been reported to be upregulated in GC patients [7]. However, the role of IL-4 in the pathogenesis of GC needs further investigation.

The gene encoding IL-4 is located on chromosome 5 (5q31.1), along with other genes for Th2 cytokines. The *IL-4* gene has about 10 Kb of base pairs which contains 4 exons [8]. The polymorphism *-590C>T* (rs2243250) in the *IL-4* gene promoter region is the most commonly reported variation of this gene, and it has multiple functions in cancer and allergic diseases [9]. Several published papers demonstrated conflicting and inconsistent results regarding the correlation of IL-4 polymorphism *-590C>T* and the prevalence of GC. Although, a good systemic review [10] has been published to show the association between *IL-4 -590C>T* polymorphism and GC susceptibility, it is important to correct a minor flaw in that paper (discussed later) and update the results with a newly published paper [11].

2. Methods

2.1. Literature search

Candidate papers were searched by using the combination of key words: (1) IL-4 or IL4, (2) "gastric cancer" or "gastric carcinoma", and (3) polymorphism or variant or mutation or genotype in the databases: PubMed, Embase, the Cochrane Library, and Google Scholar. The cut-off date was December 25th, 2015. The relevant literature were evaluated by the first and second authors independently to retrieve eligible publications. All eligible papers were subsequently agreed upon by both the first and second authors.

2.2. Inclusion and exclusion criteria

The studies involved in this meta-analysis are limited to original reports and papers that were published in a peer-reviewed journal. The diagnosis of GC in each literature fits the histological criteria. The inclusion studies are all case-control ones that included GC patients and healthy controls. The involved studies must have sufficient data to calculate odds ratios (ORs) and confidence intervals (CI) for carriage of the mutant allele(s). If the same team published more than one publication using the same case series, only the paper with the largest cohort was selected for this analysis. The exclusion criteria include: (1) no healthy control population; (2) repeated papers; (3) the study subject was not human; (4) data were not able to be extracted; and (5) the allele frequency in the control group deviated from the Hardy-Weinberge equilibrium ($p \leq 0.05$).

2.3. Data extraction

A designed data extraction form was used to abstract the data from each included publication. The following information was involved: the name of the first author; the year of publication; the country where the study occurred; the ethnicity of study participants; the age range of the study subjects (if possible); the allele frequencies; ORs and CIs; the sample size; and the clinical characteristics (if possible). All data were extracted independently by the first and second authors. The results were compared and agreed upon by all the authors.

2.4. Statistical analysis

The meta-analysis of the polled data was estimated by a fixed-effect model comparing the incidence of the *IL-4 -590T* allele (either homozygous or heterozygous) with the wild-type genotype as the reference group. Heterogeneity between studies was tested by Q and I^2 statistics. The Q test uses a X^2 distribution under the null hypothesis that there is no heterogeneity between studies ($p < 0.05$ is considered significant). The I^2 test was interpreted as the proportion of the total variation contributed by the between-study heterogeneity. A random-effects model was used for recombined data if heterogeneity exited. The deviation of published data was determined by the Hardy-Weinberg equilibrium using an online program (https://www.easycalculation.com/health/hardy-weinberg-equilibrium-calculator.php). A visual inspection of the funnel plot was used to analyze publication bias. All the processes for this meta-analysis were performed by Review Manager 5.3 software (downloaded from http://tech.cochrane.org/revman/download, 64-bit windows version).

3. Results

3.1. Publications on IL-4 -590C>T

Nine eligible publications [11–19] were identified and used for the meta-analysis. A total of 1972 cases of GC and 3226 healthy controls were involved in this analysis. All the included papers were published in English. Of these publications, 5 were based on the Asian population [11–13,17,19] and the remaining 4 studies used Caucasians as the study population [14–16,18].

3.2. Association of IL-4 -590C>T polymorphism with GC susceptibility

The Q test of heterogeneity was significant, so we used the random-effects model. We failed to observe a significant association between the T allele and GC risk in the whole population (OR = 1.13, 95%CI = 0.90–1.43, p = 0.30, Fig. 1). In order to detect the different roles of *IL-4 -590C>T* polymorphism in different ethnic populations, we also performed a meta-analysis based on the Asian population or the Caucasian population. Not surprisingly, no association of *IL-4 -590C>T* and GC susceptibility was observed in either the Asian population (OR = 1.30, 95%CI = 0.86–1.97, p = 0.21, Fig. 2) or the Caucasian population (OR = 1.07, 95%CI = 0.79–1.45, p = 0.66, Fig. 3).

4. Discussion

Inflammation plays many roles in the pathogenesis of cancer. The idea of "Cancers are wounds that never heal", which was firstly stated by Rudolph Virchow in 1858 [20], is not new. Solid tumors consist of two parts: the malignant cells themselves and stromal cells [21]. Stromal cells are also important to support tumor initiation and progression, although more interest has been concentrated on malignant cells. As a member of stroma, immune cells have key functions to modulate the tumor microenvironments. Immune cells mediate angiogenesis, immunosuppression, promotion of growth and metastasis in the tumor microenvironments by secreting cytokines, chemokines, and other factors [22]. Therefor, cytokines have gained a great of interest in their roles in the tumor microenvironment.

HP infection is the major cause of GC. Chronic HP infection is responsible for over ¾ of GC cases [23]. There is a strong correlation between GC incidence and HP infection, regardless of the histological type—Diffuse or Intestinal type [24]. During the inflammation induced by HP infection, many cytokines, chemokines, oxidative free radicals, prostaglandins, matrix metalloproteinases and growth factors are produced in the microenvironments. These factors cause DNA damage and epigenetic modifications of DNA, which induce tumorigenesis and progression [25–27]. Among cytokines, polymorphisms in the promoters of Th1 cytokines (including IL-8, tumor necrosis factor (TNF)-α and IL-1β) are related to higher susceptibility of GC in certain populations [28–30]. However, in some reports HP inflammation shows a Th2-mediated response. IL-4, a typical Th2 cytokine has been observed to be produced by dendritic cells conditioned by the medium from HP-infected gastric epithelial cells [31]. Moreover, a high proportion of IL4-producing T cells in the peripheral blood are correlated to poor prognosis in GC patients [7]. Taken together, among cytokines IL-4 plays an important role in the initiation and progression of GC.

IL-4 is an essential tumor-supporting cytokine, which plays many theoretical functions in the pathogenesis of GC. IL-4 is a typical Th2 cytokine which inhibits the anti-tumor response—Th1 inflammation and induces other anti-inflammatory cytokine production [32]. The presence of IL-4 exacerbates HP-induced inflammation in a mouse model [33]. A growing body of evidence has shown that IL-4 promotes the differentiation of AAM which support tumor growth and metastasis by increasing angiogenesis and over-expressed growth factors [34]. We recently observed that M2 cells are abundant in GC patients with peritoneal metastasis (H. Song, T. Wang and et al., unpublished observation), however whether the infiltration of M2 is caused by upregulated IL-4 in the context of GC peritoneal metastasis remains unclear. IL-4 has also been observed to suppress apoptosis in chronic lymphocytic leukemia [35], suggesting IL-4 might increase tumor growth by interrupting the proliferation/apoptosis homeostasis.

In this meta-analysis, we failed to show the association of *IL-4 -590C>T* and GC risk. According to the previous meta-analysis [10] by Sun and et al., the existence of *IL-4 -590C>T* polymorphism is a protective factor to GC in Caucasian. However, there was a flaw in that paper. The authors cited the publication of Crusisus and colleagues [14]. This case-control cohort by Crusisus and colleagues [14] contains 242 GC cases and 1154 controls, but Sun's team [14] calculated that meta-analysis with wrongly extracted *1154 GC cases and 242 controls*. Since a paper was recently published [11], a new analysis is needed. Here we report that Il-4 -590 C > T may not be related to GC risk in either Asian or Caucasian population. Several possibilities exit for this result. Firstly, published observations have relatively low volumes. Second, this polymorphism might be responsible for certain subtypes of GC. However, further well-designed studies are necessary for testing this hypothesis. Third, the microenvironment of GC is complex, many cytokines and chemokines function in the process of GC tumorigenesis. The roles of IL-4 might coordinate with other factors to promote or initiate GC. That is to say the mutation of IL-4 may function to support tumor growth only in the presence of other gene mutations. Last, this polymorphism might not be a risk factor for GC susceptibility.

The correlation between *IL-4 -590C>T* polymorphism and GC sub-type is worthy of future investigations. The polymorphism of

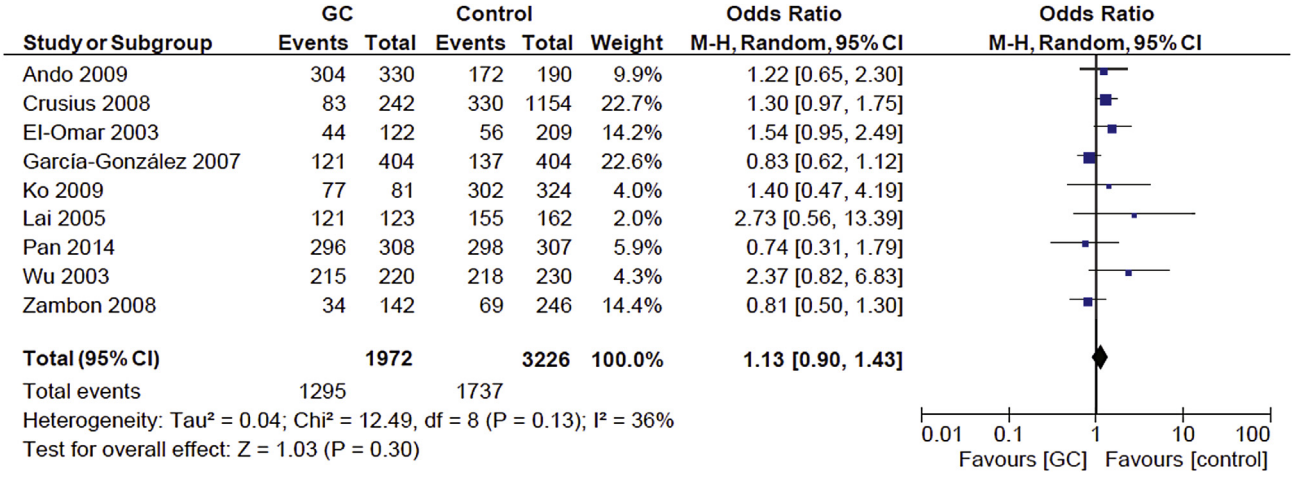

Fig. 1. The Forest Plot of ORs and 95%CI for the polymorphism *IL-4 -590 C>T* and the GC susceptibility in the entire involved studies (TT + CT v.s. CC).

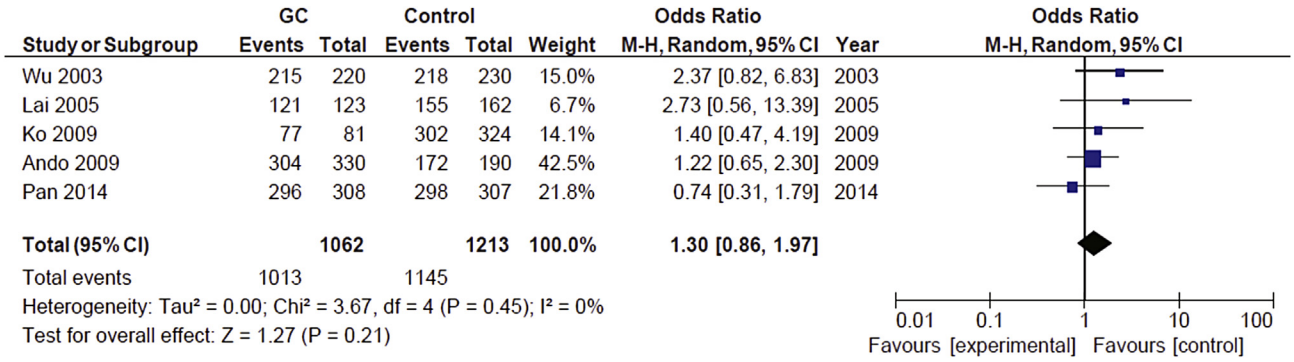

Fig. 2. The Forest Plot of ORs and 95%CI for the polymorphism *IL-4 -590 C>T* and the GC susceptibility in the studies analyzing the Asian population (TT + CT v.s. CC).

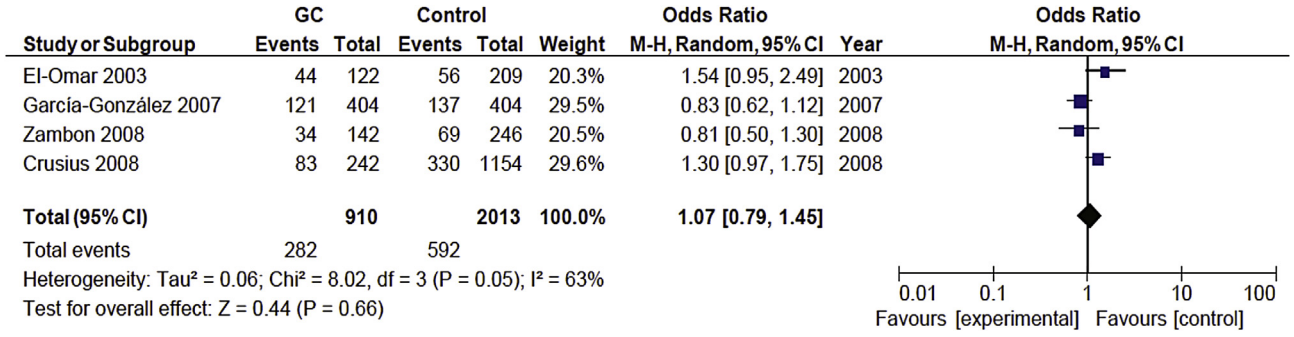

Fig. 3. The Forest Plot of ORs and 95%CI for the polymorphism *IL-4 -590 C>T* and the GC susceptibility of the investigations analyzing the Caucasian population (TT + CT v.s. CC).

IL-4 -590C>T has been investigated in cancer, infectious diseases and allergy diseases. This polymorphism exists in the promoter region of IL-4 gene and is responsible for the overproduction of IL-4 [36]. It is possible that the polymorphism of *IL-4 -590C>T* plays a supporting role in the progression in sub-types of GC. GC is divided into two major histological sub-types by Lauren's classification—Diffuse type and Intestinal type [37]. Since Diffuse type GC occurs in younger patients and has no obvious precancerous lesions, this type of GC seems more likely to be caused by genetic mutations [38]. In Diffuse type GC, the prevalence of *IL4 -590C>T* polymorphism might be higher. So far, to the best of our knowledge, no such study on the incidence of this polymorphism in Diffuse type of GC has been performed. In the future, it is reasonable to test the hypothesis that *IL-4 -590C>T* polymorphism may be related to Diffuse type GC patients.

5. Conclusion

Our results suggest the polymorphism of *IL-4 -590C>T* might not be associated with the GC susceptibility in either the Caucasian or Asian population. However, further well-designed case-control studies involving more clinical feathers are needed.

Ethical approval

Not required.

Funding

This study was supported by Heilongjiang Province Natural Science Foundation for Young Investigators (QC2011C066).

Author contribution

Dr. T. Wang designed and performed the study. All authors did literature search and agreed eligible papers. Dr. T. Wang and Dr. L. Tian extracted data from involved publications. Dr. Y. Xue directed and supervised the study.

Conflict of interest

No conflict of interest.

Guarantor

Dr. Yingwei Xue is the guarantor.

Acknowledgements

The authors would like to thank Elaine de Heuvel at the University of Calgary, Calgary, AB, Canada for reading and improving the manuscript.

References

[1] P. Bertuccio, et al., Recent patterns in gastric cancer: a global overview, Int. J. Cancer 125 (3) (2009) 666–673.
[2] H. Brenner, D. Rothenbacher, V. Arndt, Epidemiology of stomach cancer, Methods Mol. Biol. 472 (2009) 467–477.
[3] J.A. Young, et al., Reduction in gastric cancer surgical mortality over 10 years: an adverse events analysis, Ann. Med. Surg. (Lond) 3 (2) (2014) 26–30.
[4] D. Forman, V.J. Burley, Gastric cancer: global pattern of the disease and an overview of environmental risk factors, Best. Pract. Res. Clin. Gastroenterol. 20 (4) (2006) 633–649.
[5] P. Correa, J. Houghton, Carcinogenesis of Helicobacter pylori, Gastroenterology 133 (2) (2007) 659–672.
[6] S.J. Van Dyken, R.M. Locksley, Interleukin-4- and interleukin-13-mediated alternatively activated macrophages: roles in homeostasis and disease,

Annu. Rev. Immunol. 31 (2013) 317–343.
[7] H. Ubukata, et al., Evaluations of interferon-gamma/interleukin-4 ratio and neutrophil/lymphocyte ratio as prognostic indicators in gastric cancer patients, J. Surg. Oncol. 102 (7) (2010) 742–747.
[8] G.R. Sutherland, et al., Interleukin 4 is at 5q31 and interleukin 6 is at 7p15, Hum. Genet. 79 (4) (1988) 335–337.
[9] J. Zhang, et al., The -590C/T polymorphism in the IL-4 gene and the risk of cancer: a meta-analysis, Tumour Biol. 34 (4) (2013) 2261–2268.
[10] Z. Sun, et al., Association between IL-4 -590C>T polymorphism and gastric cancer risk, Tumour Biol. 35 (2) (2014) 1517–1521.
[11] X.F. Pan, et al., Interleukin-4 and -8 gene polymorphisms and risk of gastric cancer in a population in Southwestern China, Asian Pac. J. Cancer Prev. 15 (7) (2014) 2951–2957.
[12] T. Ando, et al., Synergistic effect of HLA class II loci and cytokine gene polymorphisms on the risk of gastric cancer in Japanese patients with Helicobacter pylori infection, Int. J. Cancer 125 (11) (2009) 2595–2602.
[13] K.P. Ko, et al., Soybean product intake modifies the association between interleukin-10 genetic polymorphisms and gastric cancer risk, J. Nutr. 139 (5) (2009) 1008–1012.
[14] J.B. Crusius, et al., Cytokine gene polymorphisms and the risk of adenocarcinoma of the stomach in the European prospective investigation into cancer and nutrition (EPIC-EURGAST), Ann. Oncol. 19 (11) (2008) 1894–1902.
[15] C.F. Zambon, et al., IL-4 -588C>T polymorphism and IL-4 receptor alpha [Ex5+14A>G; Ex11+828A>G] haplotype concur in selecting H. pylori cagA subtype infections, Clin. Chim. Acta 389 (1–2) (2008) 139–145.
[16] M.A. Garcia-Gonzalez, et al., Gastric cancer susceptibility is not linked to pro- and anti-inflammatory cytokine gene polymorphisms in whites: a Nationwide Multicenter Study in Spain, Am. J. Gastroenterol. 102 (9) (2007) 1878–1892.
[17] K.C. Lai, et al., Association of genetic polymorphisms of MK, IL-4, p16, p21, p53 genes and human gastric cancer in Taiwan, Eur. J. Surg. Oncol. 31 (10) (2005) 1135–1140.
[18] E.M. El-Omar, et al., Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms, Gastroenterology 124 (5) (2003) 1193–1201.
[19] M.S. Wu, et al., Interleukin-10 genotypes associate with the risk of gastric carcinoma in Taiwanese Chinese, Int. J. Cancer 104 (5) (2003) 617–623.
[20] F. Balkwill, A. Mantovani, Inflammation and cancer: back to Virchow? Lancet 357 (9255) (2001) 539–545.
[21] H.F. Dvorak, Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing, N. Engl. J. Med. 315 (26) (1986) 1650–1659.
[22] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell 140 (6) (2010) 883–899.
[23] B. Peleteiro, et al., Prevalence of Helicobacter pylori infection worldwide: a systematic review of studies with national coverage, Dig. Dis. Sci. 59 (8) (2014) 1698–1709.
[24] Y. Handa, et al., Association of Helicobacter pylori and diffuse type gastric cancer, J. Gastroenterol. 31 (Suppl 9) (1996) 29–32.
[25] R. Yasmin, et al., Epigenetic regulation of inflammatory cytokines and associated genes in human malignancies, Mediat. Inflamm. 2015 (2015) 201703.
[26] J.V. Fernandes, et al., The role of the mediators of inflammation in cancer development, Pathol. Oncol. Res. 21 (3) (2015) 527–534.
[27] S. Kawanishi, et al., Oxidative and nitrative DNA damage in animals and patients with inflammatory diseases in relation to inflammation-related carcinogenesis, Biol. Chem. 387 (4) (2006) 365–372.
[28] M. Sugimoto, et al., Different effects of polymorphisms of tumor necrosis factor-alpha and interleukin-1 beta on development of peptic ulcer and gastric cancer, J. Gastroenterol. Hepatol. 22 (1) (2007) 51–59.
[29] A. Taguchi, et al., Interleukin-8 promoter polymorphism increases the risk of atrophic gastritis and gastric cancer in Japan, Cancer Epidemiol. Biomarkers Prev. 14 (11 Pt 1) (2005) 2487–2493.
[30] E.M. El-Omar, et al., Interleukin-1 polymorphisms associated with increased risk of gastric cancer, Nature 404 (6776) (2000) 398–402.
[31] M. Kido, et al., Helicobacter pylori promotes the production of thymic stromal lymphopoietin by gastric epithelial cells and induces dendritic cell-mediated inflammatory Th2 responses, Infect. Immun. 78 (1) (2010) 108–114.
[32] S.M. Opal, V.A. DePalo, Anti-inflammatory cytokines, Chest 117 (4) (2000) 1162–1172.
[33] L.E. Smythies, et al., Helicobacter pylori-induced mucosal inflammation is Th1 mediated and exacerbated in IL-4, but not IFN-gamma, gene-deficient mice, J. Immunol. 165 (2) (2000) 1022–1029.
[34] A. Sica, P. Allavena, A. Mantovani, Cancer related inflammation: the macrophage connection, Cancer Lett. 267 (2) (2008) 204–215.
[35] I.M. Pedersen, et al., Protection of CLL B cells by a follicular dendritic cell line is dependent on induction of Mcl-1, Blood 100 (5) (2002) 1795–1801.
[36] L.J. Rosenwasser, et al., Promoter polymorphisms in the chromosome 5 gene cluster in asthma and atopy, Clin. Exp. Allergy 25 (Suppl 2) (1995) 74–78 discussion 95-6.
[37] P. Lauren, The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification, Acta Pathol. Microbiol. Scand. 64 (1965) 31–49.
[38] G. Nardone, A. Rocco, P. Malfertheiner, Review article: helicobacter pylori and molecular events in precancerous gastric lesions, Aliment. Pharmacol. Ther. 20 (3) (2004) 261–270.