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Chapter 5

The Genetic and Epigenetic Bases of Gastritis

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http://dx.doi.org/10.5772/53131

1. Introduction

Gastritis, the inflammation of the mucosal layer of the stomach, is a major clinical entity due to its association with gastric cancer and peptic ulcer disease. The primary cause of gastritis is the infection with the microaerofilic gram negative Helicobacter pylori that during the early phases elicits an acute inflammatory response which eventually evolves to a long-standing chronic gastritis (Ruggiero 2012). In the case of gastric cancer development, chronic gastritis is the first step of the so-called multistep cascade of gastric cancer. This sequence includes the non-atrophic chronic gastritis, multifocal atrophic gastritis, intestinal metaplasia, dysplasia and invasive carcinoma as were described in detail by Correa as the "human model of gastric carcinogenesis" (Fig. 1) (Correa et al. 2007). This multistep model hypothesizes that the sequence of these lesions reflects a dynamic process from a naive inflammation caused by H. pylori infection to a fully malignant neoplasm of the stomach (Correa et al. 1976; Cuello et al. 1976; Haenszel et al. 1976; Correa et al. 1990). Independent epidemiological studies have confirmed that non-atrophic, atrophic, intestinal metaplasia and dysplasia are all linked through a sequential cause-effect relationship, thus supporting the concept of a human model for gastric carcinogenesis (Ohata et al. 2004). However, the risk of malignant transformation of these lesions is poorly defined. Long-term follow-up studies have shown a risk from 10% to 17% in the case of dysplasia (Saraga et al. 1987; Coma del Corral et al. 1990; Koch et al. 1990; Whiting et al. 2002; Rugge et al. 2003). For intestinal metaplasia, the risk assessment has conflicting results and therefore a limited clinical value (Ramesar et al. 1987; Silva et al. 1990; Rokkas et al. 1991; Conchillo et al. 2001; Vannella et al. 2012). The recently developed Operative Link for Gastritis Assessment (OLGA) staging system (Rugge et al. 2007), through the evaluation of the extension and site of the atrophic changes, is an attempt to evaluate the risk of chronic gastritis to progress to intestinal metaplasia and gastric cancer (Rugge et al. 2008; Capelle et al. 2010; Rugge et al. 2010). In this scenario, the identifi-

cation of molecular bases in the multistep process of gastric carcinogenesis is highly relevant since it will contribute greatly to the risk assessments of the precursor lesions of gastric cancer. In this chapter we will primarily attempt to summarize and integrate our current knowledge of the genetic as well as epigenetic bases of the dynamic process of chronic gastritis, as well as the other entities of the so-called multistep cascade of gastric cancer.

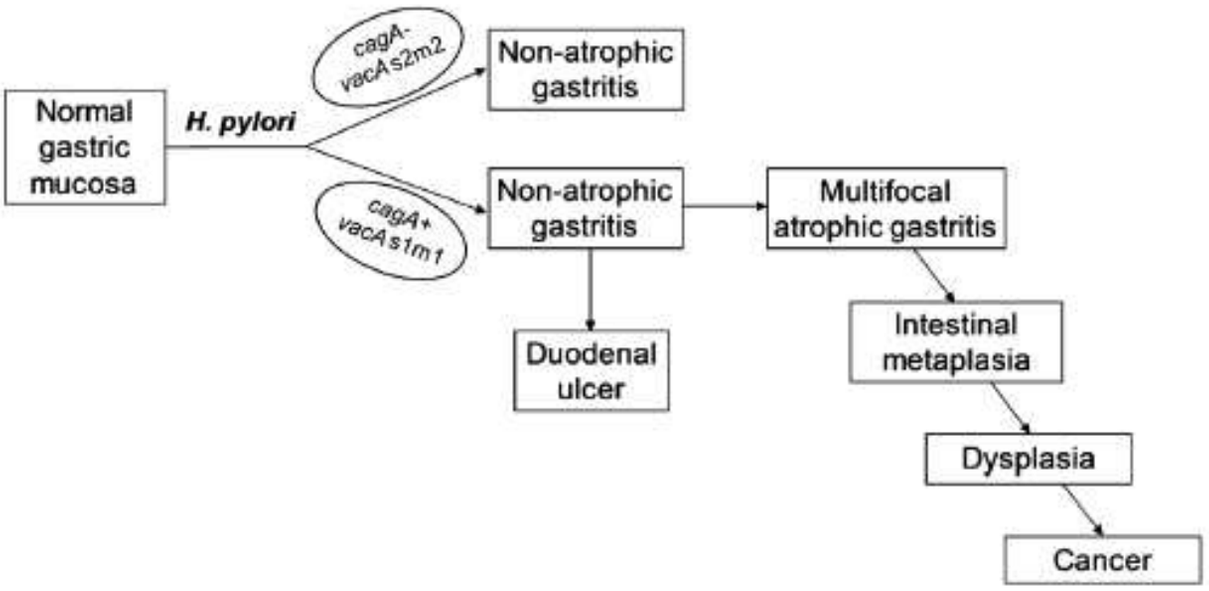

Figure 1. Multistep cascade of gastric cancer. This sequence begins with the infection of H.pylori to sequential steps of the precancerous cascades. Taken from Correa & Piazuelo J Dig Dis. 2012;13:2–9.

2. The genetic bases of gastritis

Human allelic variations at single nucleotide polymorphisms (SNP) are involved at different stages of gastric carcinogenesis. Accordingly, the dynamics of chronic gastritis might be associated with specific allelic variants. These variants, recognized as polymorphisms when occur with a frequency of >1% in the normal population, affects mostly genes of the inflammatory response genes, detoxification enzymes, and cancer-related procesess (Gonzalez et al. 2002).

Polymorphisms in inflammatory response genes

Two clear examples of polymorphisms associated with inflammatory response are interleukin-1 gene cluster and Toll-like receptors (TLRs). As shown in Table 1, Interleukin-1-beta (IL-1B) -31 T genotype and interleukin-1-receptor antagonist (IL1RN) IVS 86 bp VNTR, 2/2

genotype enhance the production of IL-1B, which is associated with an increased risk of hypochlorhydria induced by H. pylori. Because IL-1B is an important pro-inflammatory cytokine and a powerful inhibitor of gastric acid secretion, it might explain the higher risk of development of gastric cancer in chronic gastritis - H. pylori infected patients (El-Omar et al. 2000; Hwang et al. 2002; Yuzhalin 2011). The presence of polymorphisms in the non-coding but regulatory regions may also alter the levels of gene transcription and therefore the susceptibility to gastric cancer. In this sense, single A/T SNP at position -251 from the transcription start site in the promoter region of the IL-8 gene is one of the best examples. The presence of the -251A allele tended to be associated with an increase in IL-8 production and has been reported that this allele is associated with an increased risk for gastric cancer at cardia location (Hull et al. 2000; Xue et al. 2012). It could be extrapolated that IL-8 -251A allele may increase the risk of developing cancer through the elevation of its IL-8 expression. Mediators of the innate immune response, which provide first line of host defense against harmful pathogens are also involved in the dynamics of chronic gastritis. A good example for this type of inflammatory response are the Toll-like receptors (TLRs) (El-Omar et al. 2008). It has been reported that both, the 22-bp nucleotide deletion (-196 to –174 del) in the promoter region of the TLR-2 gene and the +896A/G and +1196C/T polymorphisms (Asp299Gly and Thr399Ile) in the coding region of the TLR-4 gene, promotes a rapidly progressive chronic gastritis (de Oliveira et al. 2012). Since it is well known that not all H. pylori are equally associated with the risk of development of gastric cancer, the combination of bacterial and inflammatory host genotypes have been explored. Figueiredo et al (2002) have shown that the infection with aggressive cagA-positive strains of H. pylori were associated with an increased risk of gastric cancer. In addition, the homozygous IL-1B-511*T carriers (IL-1B-511*T/*T or IL-1B-511*T/*C) and the short allele of IL-1RN (IL-1RN*2/*2) also had an increased susceptibility. However, for each combination of bacterial/host genotype, the odds of having gastric cancer were greatest in those with both bacterial and host high-risk genotypes.

Polymorphisms in genes associated with detoxification enzymes

Members of the cytochrome P-450 superfamily belong to the detoxification enzymes. One of the members of this family is the CYP2E1, a naturally ethanol-inducible enzyme involved in the metabolic activation of low molecular weight compounds such as N-nitrosamines (Boccia et al. 2007). Functional CYP2E1 polymorphisms in the 50-flanking region (PstI, RsaI) alter the transcriptional activity of the gene. A meta-analysis by Boccia et al (2007) suggests that the CYP2E1 PstI/RsaI polymorphism may be a risk factor for gastric cancer in asiatic populations and a synergic relation with tobacco-related detoxification Glutathione S-transferase (GST) genes (see below) may account for a proportion of these cases. GSTs and the polymorphic arylamine N-acetyltransferases (NAT1 and NAT2) are another type of detoxification enzymes that metabolize tobacco-related carcinogens. Zendehdel et al (2009) reported a weak linkage between the GSTP1 Ile105Val polymorphism and the risk for gastric cancer at cardia location (OR = 1.4; 95% CI 0.9-2.1). On the other hand, Katoh et al (2000) found that the NAT1*10 allele should be considered a risk factor among heavy smokers with well-differentiated tumors (Table 1).

Polymorphisms of cancer-related genes

In cancer-related processes, polymorphisms have been reported in the promoter region of the MET gene, a crucial gene to multiple oncogenic pathways and metastatic behavior (Gherardi et al. 2012). Sequencing of the promoter region of MET revealed some alterations scattered in a proportion of clinical samples of gastric cancer. The most common substitutions were -304C>A and 206C>G. The presence of these SNPs altered the junction sites for putative transcription factors such as Sp1 and AP-1/AP-2. As a consequence, the transcription of MET was constantly being activated (Trzyna et al. 2012). Another example is the polymorphism -160 A at the promoter region of the E-cadherin gene (CDH1), which has been associated with the DNA hypermethylation (see below) of the promoter region (Borges Bdo et al. 2010). In a Japanase study, 117 cases of gastric cancer with H. pylori-induced chronic gastritis were compared with 116 cancer-free yet H. pylori-induced chronic gastritis controls. It was found that the Pro/Pro allele of CDH-1 was associated with an increased risk of developing diffuse-type of gastric cancer compared to the Arg/Arg (Hiyama et al. 2002; Zhou et al. 2007). Finally, other polymorphims of cancer-related genes were reported to show significant associations with gastric cancer risk including EGFR, VEGF and p53 (Tahara et al. 2009). Taken together, data presented here suggest that allelic variations at regulatory or coding regions will affect gene expression patterns and modify the balance towards a more rapid progression of chronic gastritis and other preneoplastic lesions of the multistep cascade of gastric cancer (Fig. 2).

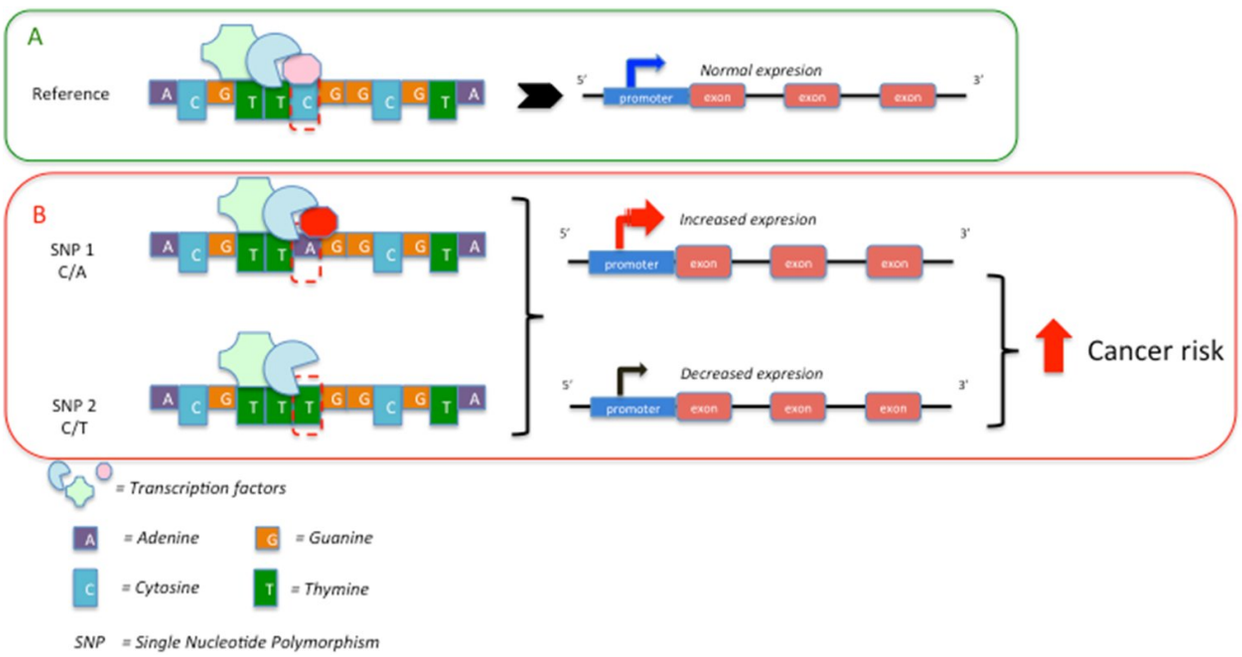

Figure 2. Allelic variations at regulatory regions will affect gene expression patterns. (A) Single nucleotide polymorphisms (SNP) in promoter region can alter the binding of transcription factors required for the expression of a gene. (B) These variations may increase or decrease the expression of the affected gene, which eventually can increase the risk of developing cancer.

Gene	Variation Allelic	SNP	rs number	Effect	Reference
IL1B	SNP	-31 T/C	rs1143627	Increased IL-1beta production and inhibit gastric acid secretion.	(Yuzhalin et al., 2011)
IL-8	SNP	-251 A/T	rs4073	Increased IL-8 production.	(Xue et al., 2012)
IL-10	SNP	-1082 A/G	rs1800896	Reported associated with the pathologically intestinal-type gastric cancer or anatomically cardia-type gastric cancer.	(Ni et al., 2012)
TLR2	Deletion	-196 to -174del	not applicable	Susceptibility to gastric cancer in the Southeastern Brazilian population.	(de Oliveira et al, 2012)
TLR4	SNP	+ 896 A/G	rs4986790		
CYP2E1	RFLP	CYP2E1 c2 allele homozygote	not applicable	Risk for gastric cancer among Asians	(Boccia et al., 2006)
GSTP1	SNP	+562 A/G	rs1695	Increased risk of esophageal squamous cell carcinoma and tended to be weakly, positively linked to cardia cancer	(Zendehdel et al., 2009)
NAT	RFLP	NAT1*10 allele	not applicable	Risk factor among the well-differentiated type of tumors of gastric cancer	(Katoh et al., 2000)
MET	SNP	-304C> A	undefined	Activate the transcription.	(Trzyna et al., 2012)
	SNP	206 C>G	undefined		
CDH1	SNP	-160 C/A	rs16260	Associated with DNA methylation linking genetic and epigenetics fields in the pathogenesis of gastritis.	(Borges Bdo et al., 2010)

Table 1. Selected single nucleotide polymorphisms (SNP) in inflammatory response genes, detoxification enzymes, and cancer-related processes associated to increase susceptibility of gastric cancer. The sign (-) indicates that the SNP is located in the direction of the promoter region, the sign (+) indicates that the SNP is located in the direction of the coding region, the number indicates the nucleotide positionfrom TSS and the first nucleotide is substituted (/) by the second.

3. Epigenetic bases of gastritis

Epigenetic processes control the packaging and function of the human genome, and contribute to normal development and disease (Callinan et al. 2006). Epigenetic mechanisms such as DNA methylation, histone modifications and microRNAs are important events toward regulating gene expression for the biology and disease of the gastrointestinal tract. In particular, DNA methylation, a process in which cytosines acquire a methyl group in the 5' position only if they are followed by a guanine (Corvalán et al. 2010), virtually affects all of the pathways in the cellular network, such as DNA repair, cell cycle, and apoptosis (Esteller et

al. 2002). Furthermore, a growing body of evidence has shown that aberrant DNA methylation (DNA hypermethylation or DNA hypomethlation) is an early event in carcinogenesis (Jones et al. 2002; Herman et al. 2003; Kopelovich et al. 2003). In addition, aberrant DNA methylation has been recently considered to be an excellent candidate to explain how certain environmental factors may increase the risk of developing cancer (Chan et al. 2006). Accordingly, an emerging catalog of cancer-related genes inactivated by DNA hypermethylation in gastric cancer has been established (Hamilton et al. 2006; Wu et al. 2006; Bernal et al. 2008). However, there are limited reports on DNA hypermethylation analysis in precursor lesions of gastric cancer. Kang et al. (2001) tested five genes (p16, hMLH1, DAP-kinase, THBS1, and TIMP-3) in precancerous conditions to identify three different classes of hypermethylated genes. Hypermethylation of DAP-kinase was found in all premalignant conditions, whereas hMLH1 and p16 were preferentially methylated in intestinal metaplasia (6.3% and 2.1%, respectively), adenomas (9.8% and 11.5%, respectively) and gastric cancer (20.3% and 42.2%, respectively). THBS-1 and TIMP-3 were also hypermethylated at a similar frequency in all premalignant conditions, but showed a marked increase from chronic gastritis to intestinal metaplasia (10.1% & 34.7% and 14.5% & 36.7%, respectively; $P < 0.05$), as well as from adenomas to carcinomas (28.3% & 48.4% and 26.7% & 57.4% respectively). Another study including 11 genes (COX-2, DAP-kinase, E-cadherin, GSTP1, MGMT, hMLH1, p14, p16, THBS1, TIMP3, and RASSF1A) and 268 premalignant conditions (Kang et al. 2003) identified specific patterns of aberrant DNA methylation associated to aging. Specifically five genes (DAP-kinase, E-cadherin, p14, THBS1, and TIMP-3) showed a progressive increase in aberrant methylation frequency as a function of aging, whereas the other genes (COX-2, GSTP1, MGMT, hMLH1, p16, and RASSF1A) were rarely methylated. Male patients showed higher numbers of hypermethylated genes than females (3.2 vs. 2.1, respectively, $P = 0.002$) and cases with severe intestinal metaplasia also showed a higher frequency of aberrantly methylated genes. Taken together, these findings suggest that hypermethylation occurs early in the multistep gastric carcinogenesis and that accumulate during this process. In addition, age and gender are closely associated with increased frequency of aberrant DNA methylation. A further study demonstrated that DNA methylation of E-cadherin was associated with H. pylori infection ($p=0.002$) in an independent way of age and/or gastritis (Chan et al. 2003). Similarly, Maekita et al. (2006) carried out a more detailed analysis of the effect of H. pylori infection in the progression of aberrant DNA methylation in chronic gastritis. These authors collected gastric mucosa samples from 154 healthy volunteers (56 H. pylori negative and 98 H. pylori positive) and from 72 cases with gastric cancers (29 H. pylori negative and 43 H. pylori positive). Among the healthy volunteers, methylation levels were 5.4- to 303-fold higher in H. pylori positive subjects than in H. pylori negative ones ($P < 0.0001$). Particularly, methylation levels of the LOX, HAND1 and THBD at their promoter regions were identified in H. pylori-positive individuals. Among H. pylori-negative individuals, methylation levels were 2.2- to 32-fold higher in gastric cancer cases than in age-matched healthy volunteers. These findings suggest that H. pylori infection potently induces aberrant DNA methylation of several genes beyond E-cadherin, and that methylation levels of specific genes seemed to reflect the risk of gastric cancer in H. pylori-negative subjects. A recent quantitative analysis of the promoter region of a novel gene Reprimo (RPRM), per-

http://dx.doi.org/10.5772/53131

formed in Colombian residents from areas with high and low incidence of gastric cancer, demonstrated an association with virulent factors such as cagA and vacA s1/m1 regions of H. pylori strains. This data suggests that certain strains of H. pylori are associated with aberrant DNA methylation on specific genes (Schneider et al. 2010). Interestingly, we have shown that Reprimo is not only found in gastric mucosa but also in the plasma of gastric cancer patients (Bernal et al. 2008). Thus, hypermethylated circulating DNA offers the opportunity for non-invasive detection of gastric cancer and premalignant gastritis (Corvalán et al. 2010; Sapari et al. 2012). As mentioned before, an aberrant of DNA methylation could be considered as a candidate to explain how environmental factors increase the susceptibility of gastric cancer. One approach to explain this phenomena could be through the evaluation of the effect of the eradication of H. pylori in the pattern of DNA methylation of the gastric mucosa. Chen et al (2003) evaluate the presence of DNA methylation of E-cadherin promoter regions before the erradication of H. pylori and after 6 weeks of treatment. DNA methylation of E-cadherin was detected in 46% (19/41) and 17% (7/41) of both untreated and treated patients, respectively. Mucosal biopsy showed chronic inactive gastritis in 35 patients, intestinal metaplasia in one patient and normal mucosa in five patients after the treatment. This data suggests that H. pylori eradication therapy could reverse aberrant DNA methylation in patients with chronic gastritis. Similar results were reported by Leung et al. (2006), although they evaluated mucosal biopsies from the antrum and corpus of H. pylori-infected subjects at the baseline, and after one year of successful H. pylori eradication. In addition, these authors identified a significant reduction in the methylated density of the promoter region of the E-cadherin gene (Leung et al. 2006). Taken together, both reports are clear examples of how the environment affects DNA methylation and shows that the eradication of H. pylori infection reverses E-cadherin promoter hypermethylation. Although less explored, DNA hypomethylation can also be involved in the risk of developing cancer. The concept of DNA hypomethylation, although identified 30 years ago (Christman et al. 1977), was overlooked in preference to DNA hypermethylation. Recently, gene activation by promoter hypomethylation has been rediscovered (Ichinose et al. 1988; Cravo et al. 1996; Fang et al. 1996; Akiyama et al. 2003; Cho et al. 2003; Mesquita et al. 2003; Oshimo et al. 2003; Chalitchagorn et al. 2004; Honda et al. 2004; Kaneda et al. 2004; Yanagawa et al. 2004; Jung et al. 2005; Nishigaki et al. 2005). Emerging data suggests that global DNA hypomethylation is thought to occur during the early stages of gastric carcinogenesis (Goelz et al. 1985; Cravo et al. 1996; Narayan et al. 1998; Lin et al. 2001; Bariol et al. 2003) but hypomethylation of individual genes, such as MAGE, synuclein-alpha, MUC2, maspin, CAGE and family A melanoma antigen (Akiyama et al. 2003; Cho et al. 2003; Mesquita et al. 2003; Honda et al. 2004; Yanagawa et al. 2004; Jung et al. 2005) is thought to occur during the advanced stages. Interestingly, overexpression of well known oncogenes, such as MYC, HRAS1 and cyclin D2 has been linked to hypomethylation in their promoter region, suggesting an inverse correlation between methylation and gene expression (Fang et al. 1996; Oshimo et al. 2003). Taken together, this data suggests that promoter hypomethylation is an underlying mechanism of gene activation that should be explored in gastric carcinogenesis. In these sense, recent work from Daskalos et al (2011) has shown that the overexpression of p73, a well stablish cancer-related gene associated with apoptosis and DNA repair (Zaika et al. 2011), might be associ-

ated with hypomethylation of the P2 promoter region that controls the DeltaNup73 isoform. Although this work was not performed in a gastric cancer model, our preliminary findings suggests similar results in gastric cancer cases (Corvalán et al. 2008). Based on both data, we decide to analysed the protein overexpression of p73 as well as other seven well stablished cancer-related genes activated by hypomethylation (BRCA1, HSP90, STAT1, FHIT, EGFR, p73, p53, p16INK4a) (Tanaka et al. 1998; Nien et al. 2007; Shutoh et al. 2009; Yu et al. 2009; Valdez et al. 2010; Daskalos et al. 2011; Rusiecki et al. 2011; Szaumkessel et al. 2011; Fornari et al. 2012). This analysis was performed in a large number of matched tumor/non-tumor adjacent mucosa of early gastric cancer as well as non-tumor cases at different stages of the multistep cascade of gastric cancer (Carrasco et al. 2010). Among 8 genes tested, only the overexpression of p73 was higher in matched tumor/non-tumor adjacent mucosa than in chronic gastritis/intestinal metaplasia (50.5% vs. 10.8%; $P < 0.0001$). We also assessed a detail histopathological analysis of the precursor lessions of gastric cancer through the Sydney and OLGA systems (Dixon et al. 1996; Corvalan et al. 2011; Rugge et al. 2011). As has been described (Rugge et al. 2010) only severe atrophy and OLGA stage IV were the most relevant features to identified high-risk gastritis (Fig. 4). However, the most interesting finding come after our attempt to integrated protein expression and histopathological assessments. This integration was performed by Significance Analysis of Microarrays (SAM), a multiple testing approach method that has been extensively applied in genomic research (Tusher et al. 2001) and confirmed by logistic regression (Nick et al. 2007). This integrative approach led us to identified that overexpression of p73 was even more significant than severe atrophy and OLGA stage IV in identifying high-risk premalignant gastritis (Carrasco et al. 2010). Therefore, we believe that the identification of the overexpression of p73 might contribute greatly to risk assessment of chronic gastritis to the development of gastric cancer.

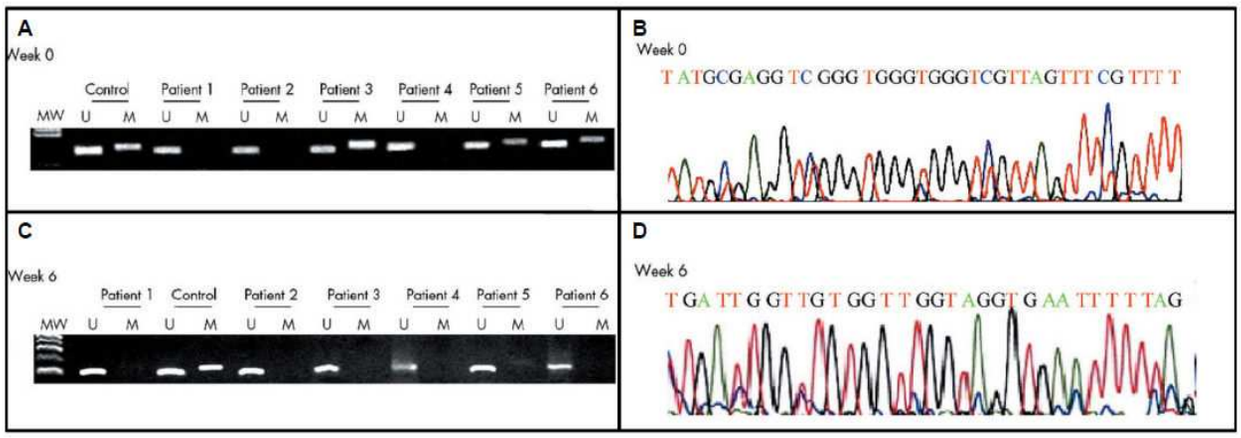

Figure 3. The effect of the eradication of H. pylori in the pattern of DNA methylation as an example of environmental factors and the susceptibility of gastric cancer. (A) Before eradication of H. pylori (week 0), methylation was present in patients 3, 5 and 6. (B) Bisulfite sequencing confirm the methylated product. (C) After eradication of H. pylori (week 6), methylation was not present in any patient. (D) Bisulfite sequencing confirm the absence of methylated cytosine. MW: molecular weight marker, U: unmethylated band, M: methylated band, red color: unmethylated cytosines converted to thymidine, blue color: methylated cytosines. Taken from Chan et al., Gut 2006;55:463-8 with permission from BMJ Publishing Group Ltd.

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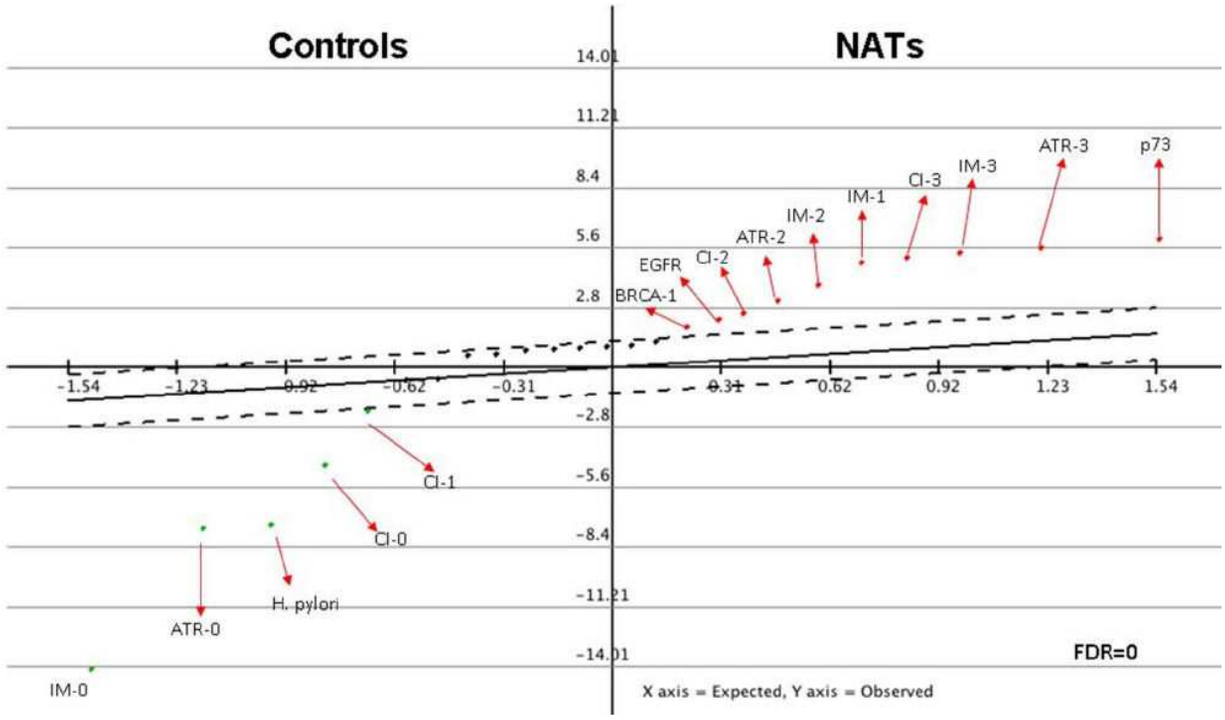

Figure 4. Serial Analysis for Microarray from Non-tumor adjacent mucosa (NTAM) and chronic gastritis controls. NTAM group is significantly characterized by the overexpression of p73, OLGA stages III to IV, and severe atrophy (ATR-3), intestinal metaplasia (IM-3), and chronic inflammation (CI-3) according to the Sydney System. Control group cases were significantly characterized by lack of intestinal metaplasia (IM-0), atrophy (ATR-0), and chronic inflammation (CI-0). False discovery rate = 0. Taken from Carrasco et al., Clin.Cancer Res 2010;16:3253-9.

4. Conclusion

Data presented here suggests that genetic, epigenetic by means of DNA methylation might play a role in the dinamics of the progression of chronic gastritis and premalignant cascade to gastric cancer. DNA methylation works in both ways, inactivating or activating tumor-related genes through the hypermethylation or hypomethylation of the promoter regions of specific genes. The integration of these molecular bases of chronic gastritis with histolopathological assessment by Sydney and OLGA systems will contribute to the better risk assessment for the development of gastric cancer.

Acknowledgements

Grant Support: Grants-in-Aid for Fondo Nacional de Ciencia y Tecnologia (FONDECYT) #1111014 and Fondo de Fomento al Desarrollo Científico y Tecnológico (FONDEF) #D09i1137 to A.H. Corvalan from the Government of Chile.

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