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REVIEW

MYC and gastric adenocarcinoma carcinogenesis

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Abstract

MYC is an oncogene involved in cell cycle regulation, cell growth arrest, cell adhesion, metabolism, ribosome biogenesis, protein synthesis, and mitochondrial function. It has been described as a key element of several carcinogenesis processes in humans. Many studies have shown an association between *MYC* deregulation and gastric cancer. *MYC* deregulation is also seen in gastric preneoplastic lesions and thus it may have a role in early gastric carcinogenesis. Several studies have suggested that amplification is the main mechanism of *MYC* deregulation in gastric cancer. In the present review, we focus on the deregulation of the *MYC* oncogene in gastric adenocarcinoma carcinogenesis, including its association with *Helicobacter pylori* (*H pylori*) and clinical applications.

Key words: *MYC*; Gastric adenocarcinoma; Gastric preneoplastic lesions; Gastric carcinogenesis; *Helicobacter pylori*

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INTRODUCTION

A temporal decline in gastric cancer (GC) incidence has been seen in several countries, including Brazil[1,2]. However, this cancer causes nearly one million deaths a year worldwide and is still a serious public health cancer[3], especially in the Pará State, Northern Brazil, where mortality rates are higher than the national average rate[2]. GC is usually diagnosed at advanced stages and the single curative therapy available requires surgical resection[4].

Over 95% of gastric malignancies are adenocarcinomas[5]. They are subdivided into two main histological types: well-differentiated or intestinal-type, and undifferentiated or diffuse-type[6]. Intestinal-type gastric tumors predominate in high-risk geographic areas whereas diffuse-type tumors are more common in low-risk areas[7].

The identification of peculiar genetic characteristics of gastric tumors may help predict prognosis of GC patients and allow more accurate therapeutic approaches. Genetic analyses of GC suggest that there occur structural and functional alterations of several oncogenes and tumor suppressor genes, as well as genetic instability[8]. Additionally, GC has been an interesting carcinogenesis model. Evidence suggests that intestinal- and diffuse-type gastric carcinomas develop through distinct genetic pathways due to different genetic alterations identified in these histological types[9,10].

MYC (*C-MYC*) oncogene has been described as a key element of several carcinogenesis processes in humans[11]. In the present review, we focus on the deregulation of the *MYC* oncogene in gastric carcinogenesis.

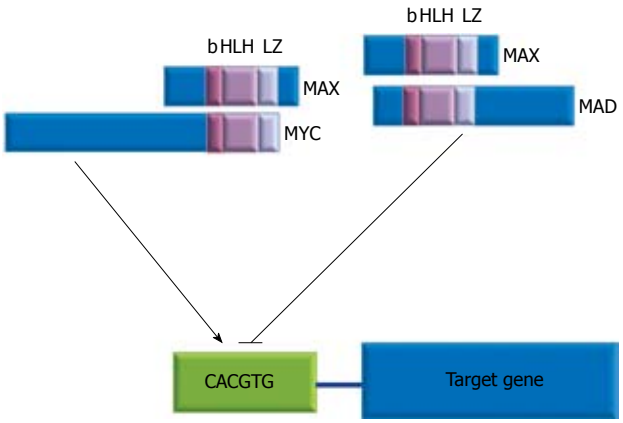

Figure 1 Activation of MYC target genes by the interaction between MYC:MAX or their repression by MAX:MAD. Domains that are common to each protein and are involved in heterodimerization are shown; b: Basic region; HLH: Helix-loop-helix; LZ: Leucine zipper. E-box sequence is shown in green.

MYC AND CANCER

MYC gene was found to be the cellular homolog of retroviral v-myc oncogene about 30 years ago[12-14]. It is located on chromosomal region 8q24.1, has 3 exons[15,16] and encodes a nuclear phosphoprotein[17].

MYC has to heteromerize with MAX, a protein expressed constitutively, to acquire DNA-binding activity. MYC/MAX dimmers are made viable by a basic region helix-loop-helix leucine-zipper motif (bHLH-Zip), conserved sequences in the carboxyl terminus of both proteins. MYC/MAX dimmers bind to E-box sequence CACGTG in the promoters of specific target genes and stimulate their transcription[18].

MYC has an effect on up to about 15% of genes in genomes of many organisms, from flies to humans[19]. Groups of genes involved in cell cycle regulation, metabolism, ribosome biogenesis, protein synthesis, and mitochondrial function are over-represented in the Myc target gene network.

MYC also consistently represses genes involved in cell growth arrest and cell adhesion[20]. Dominguez-Sola *et al*[21] recently showed that Myc interacts with the pre-replicative complex and localizes to early sites of DNA synthesis. Thus, it also has a direct role in the control of DNA replication.

MYC regulates transcription from its targets through several mechanisms, including recruitment of histone acetylases, chromatin modulating proteins, basal transcription factors and DNA methyltransferase[22-26].

Protein products of *MYC* target genes go on to mediate the downstream effects of *MYC* on cell biology. MYC is then rapidly degraded, and the pathway switches to a transcriptionally repressive state when MAX dimerizes with a group of related bHLH-Zip proteins, the MAD family, that act as MYC antagonists[27] (Figure 1).

MYC expression might be regulated transcriptionally (initiation and elongation), post-transcriptionally (mRNA stability and translation) or post-translationally (protein stability)[28].

MYC is generally recognized as an important regulator of proliferation, growth, differentiation and apoptosis[29,30]. Therefore, it is also accepted that the deregulation of *MYC* expression is a major event in cancer pathogenesis or progression. Deregulated expression of a wild-type MYC protein is sufficient to lead to cellular transformation *in vitro* and tumorigenesis *in vivo*[31].

Recent studies have also found that MYC oncoprotein, in addition to its directly transforming role, can mediate genomic instability *via* the induction of reactive oxygen species and by promoting whole chromosome instability leading to tetraploidy and aneuploidy. MYC's ability to promote chromosomal instability is closely linked to its function as a transcriptional regulator[32]. Our research group reported higher frequency of tetraploid clones in GC cell line[33] and aneuploid cells in primary gastric tumor[34,35].

Oncogenic alterations of *MYC* are commonly induced by events such as point mutations, gene amplification, chromosomal translocation, viral insertion at the *MYC* locus, and resistance of MYC protein to ubiquitin-mediated proteolysis and enhanced transcription or translation by other oncogenic signaling pathways[30].

MYC AND GASTRIC CARCINOGENESIS

MYC overexpression has been described in over 40% of GC[36]. We found that MYC protein was expressed in all cases of both intestinal- and diffuse-type gastric adenocarcinoma samples of individuals from Northern Brazil[37]. Table 1[38-59] shows the proportion of cases with *MYC* aberration in several GC studies.

Several studies have shown the association between MYC expression and histopathologic characteristics. Xu *et al*[51] and Yang *et al*[54] described a significantly higher expression of MYC in intestinal-type than in diffuse-type GC.

Kozma *et al*[50] and Yang *et al*[54] reported that higher MYC expression was associated with the presence of metastasis. Onoda *et al*[41] also found *MYC* mRNA levels were higher in metastatic than in primary lesions. Han *et al*[45] described that patients with high levels of MYC expression had poor disease-free survival. Therefore, MYC expression may represent an aggressive phenotype of GC.

MYC overexpression has also been seen in early GC when tumor invasion is confined to the mucosa or submucosa regardless of the presence of lymph node metastasis[40,41,45,46,52,54,59]. Yang *et al*[54] found a significantly higher expression of MYC in advanced GC than in early stage GC. However, Onoda *et al*[41] reported that MYC expression was found to be more frequent and stronger in early than in advanced lesions. Other studies have not found this same difference.

Several studies demonstrated an increased MYC expression in pre-cancerous gastric lesions and its increased expression also has been associated with *Helicobacter pylori* (*H pylori*) infection. *H pylori* is defined as a carcinogen factor to gastric carcinoma infection by the International Agency for Research on Cancer (IARC)[60].

Table 1 Several MYC studies in gastric cancer

Reference	Cause of MYC deregulation	Increased MYC	Number of cases	Rate (%) of cases with MYC deregulation
[38]	Overexpression	Protein	88	55
[39]	Overexpression	Protein	213	23.5
[40]	Amplification/Overexpression	DNA/Protein	31/51	12.9/41.2
[41]	Overexpression	RNA	51	68.6
[42]	Amplification	DNA	23	26
[43]	Amplification	DNA	21	48
[44]	Amplification	Protein	154	15.5
[45]	Overexpression	Protein	48 advanced/28 early	50/42
[46]	Overexpression	Protein	98 advanced/45 early	28/34
[47]	Amplification	DNA	51	24
[48]	Amplification	DNA	10	30
[49]	Overexpression	Protein	42 advanced/77 early	40.5/15.6
[50]	Amplification/Overexpression	DNA/Protein	23	26
[51]	Overexpression	Protein	30 advanced/ 6 early	63.3/50
[52]	Overexpression	Protein	35 advanced/74 early	34/16
[53]	Overexpression	Protein	84	88.1
[54]	Overexpression	Protein	63	52.4
[55]	Overexpression	Protein	65	61.5
[56]	Amplification	DNA/Protein	11	100
[37]	Amplification/Overexpression	DNA/Protein	7	100
[57]	Overexpression	Protein	204	43
[58]	Overexpression	Protein	71	42.3
[59]	Amplification/Overexpression	DNA/Protein	5 early	100

Chronic gastritis caused by *H pylori* infection may progress to intestinal metaplasia and even to GC[61,62].

Tatsuta *et al*[63] evaluated *MYC* mRNA expression by in situ hybridization in 31 elevated gastric lesions. Patients who had borderline lesions with and without *MYC* overexpression were followed up with repeated endoscopic examinations and gastric biopsies. The authors reported that well-differentiated elevated-type adenocarcinomas were detected in 46% of patients with elevated lesions that presented *MYC* overexpression during a follow-up period of about 15 mo (range, 2-32 mo) and that no cancers were found in patients with elevated lesions without *MYC* overexpression. These sample groups were significantly different. Therefore, *MYC* overexpression may provide a valuable tool for distinguishing between adenomas and well-differentiated elevated-type adenocarcinomas.

Xu *et al*[51] noticed that MYC protein expression increased progressively as follows: chronic active gastritis, gastric ulcer, mild nonclassic proliferation, severe non-classic proliferation, early GC, and progressive GC.

Lan *et al*[53] found that MYC expression was higher in GC than in chronic gastritis, intestinal metaplasia and dysplasia. MYC expression was higher in type Ⅲ intestinal metaplasia with *H pylori* compared to the same metaplasia without infection and the positive rate in dysplasia with *H pylori* was higher than that without infection. Zhang *et al*[55] also reported that MYC expression was higher in chronic atrophic gastritis with severe intestinal metaplasia than that with mild intestinal metaplasia. In chronic atrophic gastritis with severe intestinal metaplasia, MYC expression was higher in cases with *H pylori* infection than in those without infection. Higher MYC expression was also found in GC with *H pylori* infection than in that without infection. Thus, MYC expression was coordinately up-regulated in *H pylori* infected GC and chronic atrophic gastritis with severe intestinal metaplasia. Authors have suggested that *H pylori* infection may affect MYC expression in gastric diseases, especially in chronic atrophic gastritis.

Several studies have shown that patients with preneoplastic and neoplastic gastric epithelial lesions are more likely to be infected by cagA positive strains. *H pylori* cagA is one of the most virulent strains of *H pylori*. Increased cancer risk is described in individuals infected by cagA-positive *H pylori* strains compared with those infected by cagA-negative *H pylori* strains and, in general, in those living in areas with a high rate of cagA-positive *H pylori* strains[64]. Yang *et al*[54] compared MYC expression in gastric tissues (intestinal metaplasia, dysplasia and GC) with and without *H pylori* cagA. These authors found that MYC expression was significantly higher in those lesions of type Ⅲ intestinal metaplasia and dysplasia Ⅱ-Ⅲ with cagA than in those without cagA. Nardone *et al*[64] also suggested that the increased prevalence of MYC expression was in agreement with the high prevalence of cagA positivity seen in the population studied.

Kim *et al*[65] investigated the expression of MYC protein and mRNA in 22 patients with chronic gastritis who had been successfully treated for *H pylori*. Two endoscopic antral biopsies were taken before and 2 mo after *H pylori* eradication. The proportion of gastric antral epithelial cells expressing MYC protein was significantly lower after *H pylori* eradication. *MYC* mRNA expression was not changed by *H pylori* eradication. *H pylori* may affect cell cycle progression and carcinogenesis through post-translational effects on specific gene expression. Nardone *et al*[64] also found that MYC expression disappeared after *H pylori* eradication.

In vitro studies have also confirmed that *H pylori* can

affect *MYC* expression. Yang *et al*[66] described that *H pylori* induces apoptosis in human gastric adenocarcinoma cells mediated by an increased expression of *MYC* mRNA.

Epstein-Barr virus (EBV) is another infectious agent thought to contribute to cancerous transformation of human host cells. EBV infection is seen in about 10% of gastric adenocarcinoma cases[49,58,67]. Ishii *et al*[49] found MYC expression in early stages of EBV-positive GC was higher than that of EBV-negative GC, while MYC expression in advanced stages of EBV-positive GC was lower than that of EBV-negative tumors. It was inferred that EBV might cause the host cell to induce MYC expression in early cancer development, but then negatively affect MYC expression in advanced stages of cancers, making them less likely to have a natural regression *via* apoptosis. Lima *et al*[58] also reported MYC low expression in EBV-positive GC samples. However, Luo *et al*[67] have not found any correlation between EBV and MYC expression in GC, suggesting that EBV does not inhibit MYC expression in advanced stages of EBV-positive gastric cancer.

MECHANISMS OF MYC DEREGULATION IN GASTRIC CANCER

Copy number gains are frequently detected along chromosome 8 in gastric tumors[43,48,56,68-73]. Suzuki *et al*[43] described that chromosome 8 copy number was significantly higher in differentiated than undifferentiated types of GC. Our research group found 8q24.1 gain, where *MYC* is located, exclusively in intestinal subtype with metastasis by comparative genome hybridization (CGH)[72]. However, Koo *et al*[48] reported that amplifications in 8q region were more common in diffuse-type cancer.

Some studies have showed an association between MYC amplification and GC[42-44,48]. We have also previously seen *MYC* amplification in intestinal adenocarcinoma by dual-color fluorescence in situ hybridization (FISH), such as homogeneously staining chromosomal regions and double minutes, supporting our CGH results[56]. Our findings support that these two histological GC types follow different genetic pathways.

Our research group also found that all five early GC cases with MYC overexpression also had three signal to MYC gene by FISH assay, varying between 13% and 26% of cells/case[59]. Suzuki *et al*[43] found *MYC* amplification in all 6 early GC cases studied, varying between 19% and 89% of cells/case, and this rate was not significantly difference from that found in advanced GC samples. These findings suggest that *MYC* amplification can be a critical event to gastric carcinogenesis.

MYC translocation is frequently described in Burkitt's lymphoma. Few studies have also found translocation of the *MYC* locus associated with gastric carcinogenesis. Yamashita *et al*[74] identified chromosomal translocations involved in 8q24 breakpoint by spectral karyotyping (SKY) analysis of established GC cell lines and cancerous ascitic fluids. In a previous study, our findings suggested that translocations can be related to diffuse-type GC using FISH assay[37,56].

Epigenetic events play a significant role in cancer development and progression. DNA methylation is the most studied epigenetic alteration. Some studies also have demonstrated that *MYC* hypomethylation, which leads to its activation, is significantly more common in GC samples than non-cancerous tissues[75,76]. Fang *et al*[77] and Weng *et al*[78] suggest that folate level reduction is associated with upregulation of *MYC* expression and its promoter hypomethylation in GC.

FUTURE PERSPECTIVES

Proto-oncogenes have a major role not only in cancer development, but also in cancer therapies[79]. *MYC* alteration is seen in the early gastric carcinogenesis progress. The detection of *MYC* locus amplification may be used as an auxiliary tool to GC diagnosis and as a predictor of GC aggressiveness.

MYC also could be used as a therapeutical target. Several experimental studies showed that *MYC* inactivation suppresses tumors in animal models, suggesting *MYC* as a molecular target in cancer treatment[80-83].

Chen *et al*[84] evaluated the effect of MYC expression inhibition by recombinant antisense *MYC* adenovirus (Ad-ASc-myc) infected SGC7901 human gastric carcinoma cells, which have *MYC* gene amplification, in the proliferation, apoptosis and growth processes of human gastric tumors in nude mice. It was found that MYC expression inhibition may strongly inhibit cell growth and induce apoptosis in SGC7901 cells. Proliferation of Ad-ASc-myc-infected SGC7901 cells was reduced by 44.1%. Studies involving tumorigenicity in nude mice and experimental therapy in nude mice model using Ad-ASc-myc also support these findings. These studies also suggest that Ad-ASc-myc overexpression may result in the elimination of tumor cells *via* apoptosis and proliferation inhibition, and therefore reduce tumor burden.

Inhibiting MYC expression can be a potential tool for GC treatment in tumors with MYC overexpression. MYC's therapy target may help identifying more specific and less toxic therapeutic agents[30].

REFERENCES

1 **Terry MB**, Gaudet MM, Gammon MD. The epidemiology of gastric cancer. *Semin Radiat Oncol* 2002; **12**: 111-127
2 **Resende AL**, Mattos IE, Koifman S. [Gastric cancer mortality in the State of Para, Brazil, 1980-1997] *Arq Gastroenterol* 2006; **43**: 247-251
3 **World Health Organization (WHO)**. Available from: URL: http://www.who.int/en. Accessed January 29, 2008
4 **Nardone G**. Review article: molecular basis of gastric carcinogenesis. *Aliment Pharmacol Ther* 2003; **17** Suppl 2: 75-81
5 **Smith MG**, Hold GL, Tahara E, El-Omar EM. Cellular and molecular aspects of gastric cancer. *World J Gastroenterol* 2006; **12**: 2979-2990
6 **Crew KD**, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006; **12**: 354-362

7 **Hamilton SR**, Aaltonen LA. Pathology and Genetics of Tumours of the Digestive System. In: WHO Classification of Tumors. Lyon: IARC Press, 2000: 204
8 **Assumpção PP**, Burbano RR. Genética do Câncer Gástrico. 1st ed. In: Linhares E, Laércio L, Takeshi S, editors. Atualização em câncer gástrico. São Paulo: Tecmed Editora Ltda, 2005: 95-121
9 **Chan AO**, Luk JM, Hui WM, Lam SK. Molecular biology of gastric carcinoma: from laboratory to bedside. *J Gastroenterol Hepatol* 1999; **14**: 1150-1160
10 **Baffa R**, Santoro R, Bullrich F, Mandes B, Ishii H, Croce CM. Definition and refinement of chromosome 8p regions of loss of heterozygosity in gastric cancer. *Clin Cancer Res* 2000; **6**: 1372-1377
11 **Oster SK**, Ho CS, Soucie EL, Penn LZ. The myc oncogene: Marvelousl Y Complex. *Adv Cancer Res* 2002; **84**: 81-154
12 **Sheiness D**, Fanshier L, Bishop JM. Identification of nucleotide sequences which may encode the oncogenic capacity of avian retrovirus MC29. *J Virol* 1978; **28**: 600-610
13 **Bishop JM**. Retroviruses and cancer genes. *Adv Cancer Res* 1982; **37**: 1-32
14 **Vennstrom B**, Sheiness D, Zabielski J, Bishop JM. Isolation and characterization of c-myc, a cellular homolog of the oncogene (v-myc) of avian myelocytomatosis virus strain 29. *J Virol* 1982; **42**: 773-779
15 **Dalla-Favera R**, Bregni M, Erikson J, Patterson D, Gallo RC, Croce CM. Human c-myc onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells. *Proc Natl Acad Sci USA* 1982; **79**: 7824-7827
16 **Battey J**, Moulding C, Taub R, Murphy W, Stewart T, Potter H, Lenoir G, Leder P. The human c-myc oncogene: structural consequences of translocation into the IgH locus in Burkitt lymphoma. *Cell* 1983; **34**: 779-787
17 **Persson H**, Leder P. Nuclear localization and DNA binding properties of a protein expressed by human c-myc oncogene. *Science* 1984; **225**: 718-721
18 **Cowling VH**, Cole MD. Mechanism of transcriptional activation by the Myc oncoproteins. *Semin Cancer Biol* 2006; **16**: 242-252
19 **Fernandez PC**, Frank SR, Wang L, Schroeder M, Liu S, Greene J, Cocito A, Amati B. Genomic targets of the human c-Myc protein. *Genes Dev* 2003; **17**: 1115-1129
20 **Dang CV**, O'Donnell KA, Zeller KI, Nguyen T, Osthus RC, Li F. The c-Myc target gene network. *Semin Cancer Biol* 2006; **16**: 253-264
21 **Dominguez-Sola D**, Ying CY, Grandori C, Ruggiero L, Chen B, Li M, Galloway DA, Gu W, Gautier J, Dalla-Favera R. Non-transcriptional control of DNA replication by c-Myc. *Nature* 2007; **448**: 445-451
22 **McMahon SB**, Van Buskirk HA, Dugan KA, Copeland TD, Cole MD. The novel ATM-related protein TRRAP is an essential cofactor for the c-Myc and E2F oncoproteins. *Cell* 1998; **94**: 363-374
23 **Eberhardy SR**, Farnham PJ. Myc recruits P-TEFb to mediate the final step in the transcriptional activation of the cad promoter. *J Biol Chem* 2002; **277**: 40156-40162
24 **O'Connell BC**, Cheung AF, Simkevich CP, Tam W, Ren X, Mateyak MK, Sedivy JM. A large scale genetic analysis of c-Myc-regulated gene expression patterns. *J Biol Chem* 2003; **278**: 12563-12573
25 **Kanazawa S**, Soucek L, Evan G, Okamoto T, Peterlin BM. c-Myc recruits P-TEFb for transcription, cellular proliferation and apoptosis. *Oncogene* 2003; **22**: 5707-5711
26 **Brenner C**, Deplus R, Didelot C, Loriot A, Vire E, De Smet C, Gutierrez A, Danovi D, Bernard D, Boon T, Pelicci PG, Amati B, Kouzarides T, de Launoit Y, Di Croce L, Fuks F. Myc represses transcription through recruitment of DNA methyltransferase corepressor. *EMBO J* 2005; **24**: 336-346
27 **Ayer DE**, Kretzner L, Eisenman RN. Mad: a heterodimeric partner for Max that antagonizes Myc transcriptional activity. *Cell* 1993; **72**: 211-722
28 **Sears RC**. The life cycle of C-myc: from synthesis to degradation. *Cell Cycle* 2004; **3**: 1133-1137
29 **Meyer N**, Kim SS, Penn LZ. The Oscar-worthy role of Myc in apoptosis. *Semin Cancer Biol* 2006; **16**: 275-287
30 **Vita M**, Henriksson M. The Myc oncoprotein as a therapeutic target for human cancer. *Semin Cancer Biol* 2006; **16**: 318-330
31 **Chung HJ**, Levens D. c-myc expression: keep the noise down! *Mol Cells* 2005; **20**: 157-166
32 **Prochownik EV**, Li Y. The ever expanding role for c-Myc in promoting genomic instability. *Cell Cycle* 2007; **6**: 1024-1029
33 **Lima EM**, Rissino JD, Harada ML, Assumpcao PP, Demachki S, Guimaraes AC, Casartelli C, Smith MA, Burbano RR. Conventional cytogenetic characterization of a new cell line, ACP01, established from a primary human gastric tumor. *Braz J Med Biol Res* 2004; **37**: 1831-1838
34 **Costa Guimarães A**, Gonçalves Quintana L, Ferreira Leal M, Satomi Takeno S, Pimentel Assumpção P, Moura Lima E, Salim Khayat A, Suchi Chen E, de Arruda Cardoso Smith M, Rodríguez Burbano R. Aneuploidy of chromosome 8 detected by fluorescence in situ hybridisation in ACP01 cell line gastric adenocarcinoma. *Clin Exp Med* 2006; **6**: 129-133
35 **Assumpcao PP**, Seabra AD, Leal MF, Guimaraes AC, Calcagno DQ, Khayat AS, Smith MC, Burbano RR. Chromosome instability in carcinomas. *Int J Morphol* 2006; **24**: 335-338
36 **Milne AN**, Sitarz R, Carvalho R, Carneiro F, Offerhaus GJ. Early onset gastric cancer: on the road to unraveling gastric carcinogenesis. *Curr Mol Med* 2007; **7**: 15-28
37 **Calcagno DQ**, Leal MF, Seabra AD, Khayat AS, Chen ES, Demachki S, Assumpcao PP, Faria MH, Rabenhorst SH, Ferreira MV, de Arruda Cardoso Smith M, Burbano RR. Interrelationship between chromosome 8 aneuploidy, C-MYC amplification and increased expression in individuals from northern Brazil with gastric adenocarcinoma. *World J Gastroenterol* 2006; **12**: 6207-6211
38 **Spandidos DA**, Karayiannis M, Yiagnisis M, Papadimitriou K, Field JK. Immunohistochemical analysis of the expression of the c-myc oncoprotein in human stomach cancers. *Digestion* 1991; **50**: 127-134
39 **Ninomiya I**, Yonemura Y, Matsumoto H, Sugiyama K, Kamata T, Miwa K, Miyazaki I, Shiku H. Expression of c-myc gene product in gastric carcinoma. *Oncology* 1991; **48**: 149-153
40 **Nakata B**, Onoda N, Chung YS, Maeda K, Nishimura S, Yashiro M, Nitta A, Kubo T, Kato Y, Sowa M. [Correlation between malignancy of gastric cancer and c-myc DNA amplification or overexpression of c-myc protein] *Gan To Kagaku Ryoho* 1995; **22** Suppl 2: 176-179
41 **Onoda N**, Maeda K, Chung YS, Yano Y, Matsui-Yuasa I, Otani S, Sowa M. Overexpression of c-myc messenger RNA in primary and metastatic lesions of carcinoma of the stomach. *J Am Coll Surg* 1996; **182**: 55-59
42 **Hajdu J**, Kozma L, Kiss I, Szentkereszty Z, Szakall S, Ember I. Is the presence of distant metastasis associated with c-myc amplification in gastric cancer? *Acta Chir Hung* 1997; **36**: 119-121
43 **Suzuki S**, Tenjin T, Watanabe H, Matsushima S, Shibuya T, Tanaka S. Low level c-myc gene amplification in gastric cancer detected by dual color fluorescence in situ hybridization analysis. *J Surg Oncol* 1997; **66**: 173-178
44 **Hara T**, Ooi A, Kobayashi M, Mai M, Yanagihara K, Nakanishi I. Amplification of c-myc, K-sam, and c-met in gastric cancers: detection by fluorescence in situ hybridization. *Lab Invest* 1998; **78**: 1143-1153
45 **Han S**, Kim HY, Park K, Cho HJ, Lee MS, Kim HJ, Kim YD. c-Myc expression is related with cell proliferation and associated with poor clinical outcome in human gastric cancer. *J Korean Med Sci* 1999; **14**: 526-530
46 **Sanz-Ortega J**, Steinberg SM, Moro E, Saez M, Lopez JA, Sierra E, Sanz-Esponera J, Merino MJ. Comparative study of tumor angiogenesis and immunohistochemistry for p53, c-ErbB2, c-myc and EGFr as prognostic factors in gastric

cancer. *Histol Histopathol* 2000; **15**: 455-462
47 **Kitayama Y**, Igarashi H, Sugimura H. Different vulnerability among chromosomes to numerical instability in gastric carcinogenesis: stage-dependent analysis by FISH with the use of microwave irradiation. *Clin Cancer Res* 2000; **6**: 3139-3146
48 **Koo SH**, Kwon KC, Shin SY, Jeon YM, Park JW, Kim SH, Noh SM. Genetic alterations of gastric cancer: comparative genomic hybridization and fluorescence In situ hybridization studies. *Cancer Genet Cytogenet* 2000; **117**: 97-103
49 **Ishii H**, Gobe G, Kawakubo Y, Sato Y, Ebihara Y. Interrelationship between Epstein-Barr virus infection in gastric carcinomas and the expression of apoptosis-associated proteins. *Histopathology* 2001; **38**: 111-119
50 **Kozma L**, Kiss I, Hajdu J, Szentkereszty Z, Szakall S, Ember I. C-myc amplification and cluster analysis in human gastric carcinoma. *Anticancer Res* 2001; **21**: 707-710
51 **Xu AG**, Li SG, Liu JH, Gan AH. Function of apoptosis and expression of the proteins Bcl-2, p53 and C-myc in the development of gastric cancer. *World J Gastroenterol* 2001; **7**: 403-406
52 **Ishii HH**, Gobe GC, Pan W, Yoneyama J, Ebihara Y. Apoptosis and cell proliferation in the development of gastric carcinomas: associations with c-myc and p53 protein expression. *J Gastroenterol Hepatol* 2002; **17**: 966-972
53 **Lan J**, Xiong YY, Lin YX, Wang BC, Gong LL, Xu HS, Guo GS. Helicobacter pylori infection generated gastric cancer through p53-Rb tumor-suppressor system mutation and telomerase reactivation. *World J Gastroenterol* 2003; **9**: 54-58
54 **Yang GF**, Deng CS, Xiong YY, Gong LL, Wang BC, Luo J. Expression of nuclear factor-kappa B and target genes in gastric precancerous lesions and adenocarcinoma: association with Helicobactor pylori cagA (+) infection. *World J Gastroenterol* 2004; **10**: 491-496
55 **Zhang GX**, Gu YH, Zhao ZQ, Xu SF, Zhang HJ, Wang HD, Hao B. Coordinate increase of telomerase activity and c-Myc expression in Helicobacter pylori-associated gastric diseases. *World J Gastroenterol* 2004; **10**: 1759-1762
56 **Calcagno DQ**, Leal MF, Taken SS, Assumpcao PP, Demachki S, Smith Mde A, Burbano RR. Aneuploidy of chromosome 8 and C-MYC amplification in individuals from northern Brazil with gastric adenocarcinoma. *Anticancer Res* 2005; **25**: 4069-4074
57 **Milne AN**, Carvalho R, Morsink FM, Musler AR, de Leng WW, Ristimaki A, Offerhaus GJ. Early-onset gastric cancers have a different molecular expression profile than conventional gastric cancers. *Mod Pathol* 2006; **19**: 564-572
58 **Lima VP**, de Lima MA, Andre AR, Ferreira MV, Barros MA, Rabenhorst SH. H pylori (CagA) and Epstein-Barr virus infection in gastric carcinomas: correlation with p53 mutation and c-Myc, Bcl-2 and Bax expression. *World J Gastroenterol* 2008; **14**: 884-891
59 **Costa Raiol LC**, Figueira Silva EC, Mendes da Fonseca D, Leal MF, Guimaraes AC, Calcagno DQ, Khayat AS, Assumpcao PP, de Arruda Cardoso Smith M, Burbano RR. Interrelationship between MYC gene numerical aberrations and protein expression in individuals from northern Brazil with early gastric adenocarcinoma. *Cancer Genet Cytogenet* 2008; **181**: 31-35
60 **Cancer Databases and Other Resourcess**. International Agency for Research on Cancer (IARC) page. Available from: URL: http://www.iarc.fr
61 **Wu MS**, Chen SY, Shun CT, Lee WJ, Wang HP, Wang TH, Chen CJ, Lin JT. Increased prevalence of Helicobacter pylori infection among patients affected with intestinal-type gastric cancer at non-cardiac locations. *J Gastroenterol Hepatol* 1997; **12**: 425-428
62 **Wu MS**, Shun CT, Wu CC, Hsu TY, Lin MT, Chang MC, Wang HP, Lin JT. Epstein-Barr virus-associated gastric carcinomas: relation to H. pylori infection and genetic alterations. *Gastroenterology* 2000; **118**: 1031-1038
63 **Tatsuta M**, Iishi H, Baba M, Nakaizumi A, Uehara H, Taniguchi H. Expression of c-myc mRNA as an aid in histologic differentiation of adenoma from well differentiated adenocarcinoma in the stomach. *Cancer* 1994; **73**: 1795-1799
64 **Nardone G**, Staibano S, Rocco A, Mezza E, D'armiento FP, Insabato L, Coppola A, Salvatore G, Lucariello A, Figura N, De Rosa G, Budillon G. Effect of Helicobacter pylori infection and its eradication on cell proliferation, DNA status, and oncogene expression in patients with chronic gastritis. *Gut* 1999; **44**: 789-799
65 **Kim SS**, Meitner P, Konkin TA, Cho YS, Resnick MB, Moss SF. Altered expression of Skp2, c-Myc and p27 proteins but not mRNA after H. pylori eradication in chronic gastritis. *Mod Pathol* 2006; **19**: 49-58
66 **Yang Y**, Deng CS, Peng JZ, Wong BC, Lam SK, Xia HH. Effect of Helicobacter pylori on apoptosis and apoptosis related genes in gastric cancer cells. *Mol Pathol* 2003; **56**: 19-24
67 **Luo B**, Wang Y, Wang XF, Gao Y, Huang BH, Zhao P. Correlation of Epstein-Barr virus and its encoded proteins with Helicobacter pylori and expression of c-met and c-myc in gastric carcinoma. *World J Gastroenterol* 2006; **12**: 1842-1848
68 **Sakakura C**, Mori T, Sakabe T, Ariyama Y, Shinomiya T, Date K, Hagiwara A, Yamaguchi T, Takahashi T, Nakamura Y, Abe T, Inazawa J. Gains, losses, and amplifications of genomic materials in primary gastric cancers analyzed by comparative genomic hybridization. *Genes Chromosomes Cancer* 1999; **24**: 299-305
69 **Panani AD**, Ferti AD, Avgerinos A, Raptis SA. Numerical aberrations of chromosome 8 in gastric cancer detected by fluorescence in situ hybridization. *Anticancer Res* 2004; **24**: 155-159
70 **Kitayama Y**, Sugimura H. Nonrandom chromosomal numerical abnormality as a new molecular cytogenetic tumor marker--a retrospective study of 60 gastric cancer cases. *Rinsho Byori* 2005; **53**: 881-886
71 **Assumpcao PP**, Ishak G, Chen ES, Takeno SS, Leal MF, Guimaraes AC, Calcagno DQ, Khayat AS, Demachki S, Smith Mde A, Burbano RR. Numerical aberrations of chromosome 8 detected by conventional cytogenetics and fluorescence in situ hybridization in individuals from northern Brazil with gastric adenocarcinoma. *Cancer Genet Cytogenet* 2006; **169**: 45-49
72 **Burbano RR**, Assumpcao PP, Leal MF, Calcagno DQ, Guimaraes AC, Khayat AS, Takeno SS, Chen ES, De Arruda Cardoso Smith M. C-MYC locus amplification as metastasis predictor in intestinal-type gastric adenocarcinomas: CGH study in Brazil. *Anticancer Res* 2006; **26**: 2909-2914
73 **Yang S**, Jeung HC, Jeong HJ, Choi YH, Kim JE, Jung JJ, Rha SY, Yang WI, Chung HC. Identification of genes with correlated patterns of variations in DNA copy number and gene expression level in gastric cancer. *Genomics* 2007; **89**: 451-459
74 **Yamashita Y**, Nishida K, Okuda T, Nomura K, Matsumoto Y, Mitsufuji S, Horiike S, Hata H, Sakakura C, Hagiwara A, Yamagishi H, Taniwaki M. Recurrent chromosomal rearrangements at bands 8q24 and 11q13 in gastric cancer as detected by multicolor spectral karyotyping. *World J Gastroenterol* 2005; **11**: 5129-5135
75 **Fang JY**, Zhu SS, Xiao SD, Jiang SJ, Shi Y, Chen XY, Zhou XM, Qian LF. Studies on the hypomethylation of c-myc, c-Ha-ras oncogenes and histopathological changes in human gastric carcinoma. *J Gastroenterol Hepatol* 1996; **11**: 1079-1082
76 **Fang JY**, Cheng ZH, Chen YX, Lu R, Yang L, Zhu HY, Lu LG. Expression of Dnmt1, demethylase, MeCP2 and methylation of tumor-related genes in human gastric cancer. *World J Gastroenterol* 2004; **10**: 3394-3398
77 **Fang JY**, Xiao SD, Zhu SS, Yuan JM, Qiu DK, Jiang SJ. Relationship of plasma folic acid and status of DNA methylation in human gastric cancer. *J Gastroenterol* 1997; **32**: 171-175
78 **Weng YR**, Sun DF, Fang JY, Gu WQ, Zhu HY. Folate

levels in mucosal tissue but not methylenetetrahydrofol ate reductase polymorphisms are associated with gastric carcinogenesis. *World J Gastroenterol* 2006; **12**: 7591-7597

79 **Gschwind A**, Fischer OM, Ullrich A. The discovery of receptor tyrosine kinases: targets for cancer therapy. *Nat Rev Cancer* 2004; **4**: 361-370

80 **Boxer RB**, Jang JW, Sintasath L, Chodosh LA. Lack of sustained regression of c-MYC-induced mammary adenocarcinomas following brief or prolonged MYC inactivation. *Cancer Cell* 2004; **6**: 577-586

81 **Shachaf CM**, Kopelman AM, Arvanitis C, Karlsson A, Beer S, Mandl S, Bachmann MH, Borowsky AD, Ruebner B, Cardiff RD, Yang Q, Bishop JM, Contag CH, Felsher DW. MYC inactivation uncovers pluripotent differentiation and tumour dormancy in hepatocellular cancer. *Nature* 2004; **431**: 1112-1117

82 **Shachaf CM**, Felsher DW. Tumor dormancy and MYC inactivation: pushing cancer to the brink of normalcy. *Cancer Res* 2005; **65**: 4471-4474

83 **Yu D**, Dews M, Park A, Tobias JW, Thomas-Tikhonenko A. Inactivation of Myc in murine two-hit B lymphomas causes dormancy with elevated levels of interleukin 10 receptor and CD20: implications for adjuvant therapies. *Cancer Res* 2005; **65**: 5454-5461

84 **Chen JP**, Lin C, Xu CP, Zhang XY, Fu M, Deng YP, Wei Y, Wu M. Molecular therapy with recombinant antisense c-myc adenovirus for human gastric carcinoma cells in vitro and in vivo. *J Gastroenterol Hepatol* 2001; **16**: 22-28

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