**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.

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**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 problem[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[5].

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[7]. 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[6,8].

**MYC (C-MYC) oncogene has been described as a key element of several carcinogenesis processes in humans[9].** In the present review, we focus on the deregulation of the MYC oncogene in gastric carcinogenesis.
MYC AND CANCER

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

**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.

**MYC** has an effect on up to about 15% of genes in genomes of many organisms, from flies to humans.

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. Dominguez-Sola et al. 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.

**Product** proteins 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 (Figure 1).

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

**MYC** is generally recognized as an important regulator of proliferation, growth, differentiation and apoptosis. 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.

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.

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.

MYC AND GASTRIC CARCINOGENESIS

**MYC** overexpression has been described in over 40% of GC. We found that **MYC** protein was expressed in all cases of both intestinal- and diffuse-type gastric adenocarcinoma samples of individuals from Northern Brazil. Table 1 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. and Yang et al. described a significantly higher expression of **MYC** in intestinal-type than in diffuse-type GC.

Kozma et al. and Yang et al. reported that higher **MYC** expression was associated with the presence of metastasis. Onoda et al. also found **MYC** mRNA levels were higher in metastatic than in primary lesions. Han et al. 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. Yang et al. found a significantly higher expression of **MYC** in advanced GC than in early stage GC. However, Onoda et al. 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).
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\(^{[64]}\) noticed that MYC protein expression increased progressively as follows: chronic active gastritis, gastric ulcer, mild nonclassic proliferation, severe nonclassic proliferation, early GC, and progressive GC.

Lan et al\(^{[65]}\) 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\(^{[66]}\) 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\(^{[67]}\). Yang et al\(^{[68]}\) 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\(^{[69]}\) 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\(^{[70]}\) 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. *H. pylori* may affect cell cycle progression and carcinogenesis through post-translational effects on specific gene expression. Nardone et al\(^{[71]}\) also found that MYC expression disappeared after *H. pylori* eradication.

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

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**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                                    |
| [57]      | Amplification/Overexpression | DNA/Protein  | 7              | 100                                    |
| [58]      | Overexpression           | Protein       | 204            | 43                                     |
| [59]      | Overexpression           | Protein       | 71             | 42.3                                   |
| [59]      | Amplification/Overexpression | DNA/Protein  | 5 early        | 100                                    |
affect MYC expression. Yang et al[40] 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[56] also reported MYC low expression in EBV-positive GC samples. However, Luo et al[57] 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 DEREGLURATION IN GASTRIC CANCER

Copy number gains are frequently detected along chromosome 8 in gastric tumors[45,48,56,68-73]. Suzuki et al[48] 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[32,41,48]. 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[64]. 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[37]. Suzuki et al[40] found MYC amplification in all 6 early GC cases studied, varying between 19% and 89% of cells/case, and this rate was not significantly different 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[58] 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[37,59].

Epigenetic events play a significant role in cancer development and progression. DNA methylation is the most studied epigenetic alteration. Some studies have also demonstrated that MYC hypomethylation, which leads to its activation, is significantly more common in GC samples than non-cancerous tissues[57,58]. Fang et al[57] and Weng et al[59] 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 process. 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 therapeutic target. Several experimental studies showed that MYC inactivation suppresses tumors in animal models, suggesting MYC as a molecular target in cancer treatment[60-63].

Chen et al[64] 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[83].

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