The Complex Network between MYC Oncogene and microRNAs in Gastric Cancer: An Overview

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Abstract: Despite the advancements in cancer treatments, gastric cancer is still one of the leading causes of death worldwide. In this context, it is of great interest to discover new and more effective ways of treating this disease. Accumulated evidences have demonstrated the amplification of 8q24.21 region in gastric tumors. Furthermore, this is the region where the widely known MYC oncogene and different microRNAs are located. MYC deregulation is key in tumorigenesis in various types of tissues, once it is associated with cell proliferation, survival, and drug resistance. microRNAs are a class of noncoding RNAs that negatively regulate the protein translation, and which deregulation is related with gastric cancer development. However, little is understood about the interactions between microRNAs and MYC. Here, we overview the MYC role and its relationship with the microRNAs network in gastric cancer aiming to identify potential targets useful to be used in clinic, not only as biomarkers, but also as molecules for development of promising therapies.

Keywords: gastric cancer; microRNA; 8q24.21; MYC; target therapy

1. Introduction

Gastric cancer (GC) is one of the most common cancers worldwide, and its incidence is very high mainly in Eastern Asia, Eastern Europe, and South America [1,2]. In 2018, the Global Cancer Observatory (GLOBOCAN) estimated 1,033,701 new cases of stomach neoplasms worldwide, representing 5.7% of all new cases of cancer. Additionally, gastric tumors were expected to be the 3rd cause of cancer related death among males and the 5th among females, evidencing that GC is more likely to be diagnosed in males than in females. Collectively, between men and women, stomach cancer was predicted to correspond to 782,685 deaths and be the 7th most prevalent neoplasm. Moreover, for 2018, globally,
the risk of developing stomach cancer was 1.87% in men and 0.79% in women. While the risk of dying because of stomach cancer was 1.36% for males and 0.57% for females [3]. GC is an aggressive disease commonly diagnosed at advanced stages, and surgical resection associated with chemotherapy or chemoradiation is considered the main treatment option for GC [4]. The etiology of GC is multifactorial including environmental factors, such as Helicobacter pylori (H. pylori) infection [5] and Epstein–Barr virus infection [6], dietary factors [7,8], high consumption of alcohol [9], smoking [10], as well as genetic factors [11], and epigenetic alterations [12,13].

Chromosome 8 regions are frequently amplified in GC samples, especially the 8q24.21 region [14–17]. Among the coding genes present in this region, the most studied is MYC (also named c-MYC; Figure 1), and the literature shows that its activation can contribute to tumorigenesis [18–20]. MYC amplification and its upregulated expression have been commonly observed in GC cell lines and GC tissues, and the highest MYC levels have been reported in the tumors of patients with local or distant metastasis [14,17,21–29]. The key role of MYC in GC etiology was further confirmed in a nonhuman primate model, where both MYC expression and copy number were continuously increased during the sequential steps of intestinal-type gastric carcinogenesis [26]. Indeed, MYC not only has a key role in gastric carcinogenesis but is also one of the most robust and significant prognostic markers of GC [16]. For this reason, further topics will explore more of this role.

**Figure 1.** The 8q24.21 genes. The coding genes are shown in green, and the non-coding genes in grey.
It is worth mentioning other coding and noncoding genes of 8q24.21, shown in Table 1. Among them, the plasmacytoma variant translocation 1 (PVT1) oncogene encodes a long noncoding RNA (lncRNA). Compared with MYC, PVT1 is less studied, but it is involved in critical processes in cancer cells, including DNA rearrangements, genetic instability, microRNA (miRNA) encoding, and also interacts with MYC itself [30–33]. Increased PVT1 expression was shown to induce cell proliferation and migration in GC cell lines, and it was previously associated with higher cell invasion, advanced stages, and poor prognosis in GC patients [34–36]. Besides PVT1, the CASC11 noncoding gene is highly expressed in GC tissues and cell lines, and its knockdown inhibits cancer progression [37–42].

| Table 1. Genes localized at 8q24.21 region. |
|-------------------------------------------|
| Gene          | Gene Name Description | Expression in GC | Reference |
|----------------|------------------------|------------------|-----------|
| Coding genes  |                        |                  |           |
| FAM84B        | Family with sequence similarity 84, member B | ?                |           |
| POUSF1B       | POU domain, class 5, transcription Factor 1B | Down             | [42]      |
|               |                        | Up               | [41]      |
| MYC           | MYC proto-oncogene      | Up               | [14,16,21,22,24–27,43–45] |
| GSDMC         | Gaspdermin C            | ?                |           |
| FAM49B        | Family with sequence similarity 49 member B | ?                |           |
| ASAP1         | ArfGAP with SH3 domain, ankyrin repeat and PH domain 1 | ?                |           |
| Noncoding genes |                        |                  |           |
| CASC8         | Cancer susceptibility candidate 8 | ?                | [46]      |
| CASC11        | Cancer susceptibility candidate 11 | Up               | [37]      |
| CASC21        | Cancer susceptibility candidate 21 | ?                |           |
| CASC19        | Cancer susceptibility candidate 19 | ?                |           |
| CCAT1         | Colon cancer-associated transcript 1 | Up               | [38,39]   |
| CCAT2         | Colon cancer-associated transcript 2 | Up               | [40]      |
| LINC00824     | Long intergenic non-protein coding RNA 824 | ?                |           |
| LINC00977     | Long intergenic non-protein coding RNA 977 | ?                |           |
| miR-1204      | MicroRNA 1204 | ?                |           |
| miR-1205      | MicroRNA 1205 | Did not differ   | [47]      |
| miR-1206      | MicroRNA 1206 | ?                |           |
| miR-1207      | MicroRNA 1207 | Did not differ   | [47]      |
| miR-1208      | MicroRNA 1208 | Did not differ   | [47]      |
| miR-5194      | MicroRNA 5194 | ?                |           |
| miR-3686      | MicroRNA 3686 | ?                |           |
| CCDC26        | Coiled-coil domain-containing protein 26 | ?                |           |
| TEMEM75       | Transmembrane protein 75 | ?                |           |
| PCAT1         | Prostate cancer-associated transcript 1 | ?                |           |
| PCAT2         | Prostate cancer-associated transcript 2 | ?                |           |
| PRNCR1        | Prostate cancer associated noncoding RNA 1 | ?                | [48]      |
| PVT1          | Plasmacytoma variant translocation 1, MYC activator | Up               | [49]      |

GC: gastric cancer; Up, upregulated expression in gastric cancer in relation to control; Down, downregulated expression in gastric cancer in relation to nonneoplastic samples; Did not differ, expression in gastric cancer did not differ in relation to nonneoplastic samples; ?: absence of studies on direct relationship between the respective microRNA and MYC in gastric cancer.

Some miRNAs (Table 1) were also identified in the 8q24.21 region. miRNA is a molecular class of small noncoding RNA of approximately 22 nucleotides that regulate gene expression through sequence complementarity with the target mRNA. miRNA genes are transcribed into primary miRNA transcripts and subsequently processed by the RNase III enzyme Drosha inside the nucleus, releasing 60-110-nucleotide pre-miRNA hairpins. The pre-miRNA is then exported into the cytoplasm by Exportin-5, where it is cleaved by Dicer into ~22-nucleotide double-stranded miRNAs. Finally, miRNAs regulate the expression of their mRNA targets when the multiprotein RNA-induced silencing complex (RISC) is formed [50]. In this process, total complementarity results in the cleavage of the mRNA target strand, while imperfect complementarity leads to repression of the mRNA translation [51]. Thus, unsurprisingly, miRNA deregulation has been described in different diseases, including GC [47,52], and this deregulation may help us elucidate critical pathways involved in carcinogenesis processes and identify potential prognostic or predictive biomarkers [53–56].
Notably, a variety of miRNAs can also directly or indirectly regulate MYC expression [57,58]. Therefore, the complex interaction between MYC and miRNAs still needs to be further understood. This review updates and illustrates the oncogenic role of MYC in gastric carcinogenesis and its association with *H. pylori* infection, highlighting the network with miRNAs.

2. Biological Significance of MYC

The MYC family is a group of cellular proto-oncogenes with the following three highly related nuclear phosphoproteins: MYC, N-MYC, and L-MYC [59]. MYC has a low expression and has a short half-life in normal cells, and its mRNA level is tightly regulated by both transcriptional and post-transcriptional mechanisms [60]. However, it is overexpressed in several neoplasms. Our group and others have shown MYC overexpression in GC samples [17,43,44], including early stages [23,61], and reported MYC protein overexpression [23,24]. Moreover, other studies revealed the importance of the co-amplification of MYC and *EGFR* and *FGFR2*, in predicting poor survival of patients undergoing cancer therapy [62]. In tumor cells, MYC activation occurs as follows: (1) mutations in signaling pathways proteins upstream from MYC; (2) mutations and single nucleotide polymorphisms in regulatory regions that enhance the stability of these proteins [63] and (3) direct modification of MYC gene via gene amplification, mutation, chromosomal translocation and epigenetic modifications [24,63–65].

MYC deregulation plays an important role in neoplastic development by targeting genes involved in critical cellular functions, such as DNA metabolism and dynamics, cell cycle, apoptosis, adhesion, survival, and protein and macromolecular synthesis [60,66,67]. Moreover, it contributes to aerobic metabolism by activating the expression of several genes essential for glycolysis and mitochondrial biogenesis [68]. Additionally, its hyperactivity can allow widespread miRNAs downregulation through the regulation of transcriptional and post-transcriptional mechanisms. Indeed, MYC is known as the gene with the highest interaction with downregulated miRNAs [69–71]. Taken together, this scenario shows that MYC deregulation (usually overexpression) can have an impact in various cellular functions, contributing to an abnormal cell growth (Figure 2) [68,72].

![Figure 2. Pleiotropic consequence of MYC deregulation in cancer. MYC overexpression in gastric carcinogenesis affects various components of signaling pathways critical to cancer establishment. Some of these pathways’ phenotypes are shown here.](image-url)

Infectious agents are extremely important factors on cancer development, accounting for 16% of all new cancer cases per year worldwide [73]. Moreover, liver and gastric tumors in men account for greater than 80% of the infection-related burden cancers [73]. According to the International Agency for Research on Cancer (IARC), 78% of all GC cases are estimated to be associated to chronic *H. pylori* infection.
*H. pylori* infection, a bacteria classified as a group 1 carcinogen [74]. The virulence of this bacterium is commonly determined by *cagA* and *vacA* genes. The *cagA* gene encodes the secretion complex, capable of introducing the cagA oncoprotein in the gastric epithelial cell, which activates mitogen-activated protein (MAP) kinases. This alteration activates cell proliferation, differentiation, and stress and inflammatory responses and inhibits programed death, leading to a precancerous process [75,76]. Especially in intestinal-type of GC, *H. pylori cagA* has been associated with increased *MYC* expression and nuclear MYC protein [77,78]. In *H. pylori* infected patients with active gastritis, chromosomal aneuploidy and cellular DNA damage were associated with *MYC* expression, leading to a chronic hyperproliferation [79]. This association may occur through *H. pylori*-induced activation of NF-κB and AP-1 proteins which transcriptionally regulate β-catenin expression, responsible for controlling *MYC* expression and consequently cell proliferation [67,80]. On the other hand, *MYC* overexpression was not observed in patients without *H. pylori* infection [79].

The alteration of the DNA methylation profile is considered to be associated with the *H pylori* inflammatory response, rather than the infection itself [81]. This infection participates in the regulation of *MYC* expression, which is necessary to gastric carcinogenesis occur (Figure 3), but its infection alone is insufficient to the disease establishment. Thus, the identification of molecules and miRNAs associated with *H. pylori* infection in GC can contribute to understand the key cellular and molecular processes at the beginning of carcinogenesis and how environmental factors contribute to GC etiology.

![Figure 3](image-url)  
Figure 3. Pathways scheme in which miRNAs regulate MYC and PVT1 expression and vice versa in neoplastic gastric tissue samples and cell lines. The coding genes are shown in green, and the non-coding genes in grey. Lines ending with an arrow indicate activation, whereas T ending lines indicate repression. Lines with a red cross indicate that the interaction is lost due to repression or blocking of a miRNA or protein.

3. The Complex Relationship between microRNAs and MYC Expression

The deregulation of the expression of several miRNAs can directly or indirectly lead to increased or decreased *MYC* (Table 2). As described above, *MYC* plays a key role in the normal and tumor development, and the MYC/miRNA network is likely to contribute to the oncogenic functions of MYC. In the present review, we highlight some miRNAs that are altered in GC and are associated with *MYC* activation.
Table 2. Deregulated miRNAs associated directly or indirectly with MYC expression in gastric cancer.

| miRNA           | Expression | MYC Expression | Reference |
|-----------------|------------|----------------|-----------|
| miR-9           | Up         | Up             | [82,83]   |
| miR-15a/16-1    | Down       | Up             | [84,85]   |
| miR-25          | Up         | Up             | [86,87]   |
| miR-17          | Up         | Up             | [87,88]   |
| miR-18a         | Up         | Up             | [87,89]   |
| miR-19a/miR-19b | Up         | Up             | [87,90]   |
| miR-20          | Up         | ?              | [87]      |
| miR-22          | Down       | ?              | [91]      |
| miR-26          | Down       | Up             | [92]      |
| miR-29          | Down       | ?              | [93]      |
| miR-33b         | Down       | Down           | [94]      |
| miR-34a         | Down       | Up             | [95,96]   |
| miR-92          | Down       | ?              | [97]      |
| miR-93          | Up         | Down           | [98]      |
| miR-101         | Down       | Up             | [99]      |
| miR-106a/miR-106b | Up     | ?              | [87,100]  |
| miR-150         | Down       | Up             | [101]     |
| miR-152         | Down       |               | [102]     |
| miR-185         | Down       | Up             | [103]     |
| miR-186         | Down       | ?              | [104]     |
| miR-200c        | Down       | ?              | [105]     |
| miR-212         | Up         | Up             | [106]     |
| miR-363         | Down       | Up             | [106]     |
| miR-374         | Up         | ?              | [107]     |
| miR-429         | Down       | Up             | [108]     |
| miR-494         | Down       | Up             | [109]     |
| miR-520d-3p     | Down       | Up             | [110]     |
| miR-561         | Down       | Up             | [111]     |
| miR-935         | Up         | Up             | [112]     |
| miR-1284        | Down       | ?              | [113]     |
| let-7a          | Up         | Up             | [114]     |

Up, upregulated expression in gastric cancer in relation to control; Down, downregulated expression in gastric cancer in relation to control; ?: absence of studies on direct relationship between the respective microRNA and MYC in gastric cancer.

3.1. MYC Is Regulated by Epigenetic Modifications

Epigenetic modifications are involved in most cellular biological processes by the regulation of coding and noncoding gene expression. The term epigenetic is defined as heritable modifications in gene expression with no change in the sequence of DNA nucleotides. Notably, MYC and miRNAs expressions are regulated by epigenetic mechanisms, such as promoter methylation and histone acetylation. For instance, miR-212 expression is downregulated by its promoter methylation in GC patient tissues and cell lines. MYC mRNA expression is upregulated upon miR-212 knockdown. Additionally, experiments using wild type and mutant miR-212 mimics and luciferase activity assays confirmed that MYC is a target of miR-212 [115]. Another example is miR-33b, which is downregulated in GC, and its expression can also be inhibited by the hypermethylation of its promoter [116]. Additionally, ectopic expression of miR-33b inhibits tumorigenesis in vitro and in vivo by directly targeting MYC, indicating that this miRNA plays a tumor suppressor role in GC (Table 2) [116]. Hayashi et al. showed that the aforementioned H. pylori cagA inhibits let-7 expression and enhances the expression of MYC DNA methyltransferase 3B (DNMT3B) and Enhancer of Zeste homologue 2 (EZH2). As a result, let-7 expression was decreased due to methylation of its promoter and increased H3K27 trimethylation [77]. MiR-448 is another miRNA reported to control MYC expression by epigenetic modifications. Hong et
al. showed that miR-448 expression is up-regulated in GC cell lines and patient samples compared to a normal gastric mucous cell line and paired non-tumor tissues. The overall survival and the time to relapse of GC patients with higher miR-448 expression was reported shorter when compared with the GC patients with low miR-448. Consistently, the group of GC tumors with high miR-448 expression was associated with poor histological differentiation, tumor size and distant metastasis. In vitro and in vivo experiments demonstrated that miR-448 promotes proliferation by repressing KDM2B (Lysine Demethylase 2B) stimulating glycolysis. Furthermore, KDM2B was shown to be bound to MYC promoter inhibiting its expression, demonstrating that KDM2B suppression by miR-448 is essential for the overexpression of MYC expression in GC [117]. A study by Choi et al. revealed that Mir-185 and GKN1 (Gastrokine 1) expression levels were reduced in gastric mucosal samples, while protein expression levels of DNMT1, EZH2, and MYC were higher in these samples. Analysis of CpG island methylation showed that mir-185 and GKN1 promoters are highly methylated, whereas DNMT1, EZH2, and MYC promoters are less methylated. Suggesting that mir-185 may regulate DNMT1, EZH2, and MYC expression [118]. Collectively, these data suggest that besides epigenetic alterations in its gene, MYC expression is also influenced by epigenetic alterations in miRNAs genes.

3.2. MicroRNAs Regulate MYC Oncogenic Pathways

MYC is involved in several pathways in gastric tumor cells (Figure 2), and manifold miRNAs may interfere with them, such as miR-494, miR-429, miR-520d-3p, miR-363, miR-561 and the aforementioned miR-33b. In GC, miR-494 and miR-429 are downregulated, and negatively correlated with MYC expression. The overexpression of miR-494 decreased MYC expression, the number of viable cancer cells, tumor burden, and the percentage of proliferative cells [109], and cells transfected with miR-429 showed downregulation of MYC protein [108]. miR-520d-3p, which is also downregulated in GC tissue and cell lines, inhibited the expression of EphA2 (Ephrin Receptor A2), a gene involved in nervous system development. Additionally, cells transfected with mimic miR-520d-3p showed lower MYC and EphA2 expression and diminished cell proliferation, invasion, and migration [110,119]. miR-363 promotes GC progression through MBP-1 inhibition, leading to an upregulation of MYC protein expression [106]. miR-561 is also downregulated in human GC cell lines and tissues, and its expression was associated with tumor-node-metastasis (pTNM) staging system and suppressed MYC expression by directly binding to its 3′-untranslated region [111]. This research group demonstrated that miR-561 can act as a tumor suppressor miRNA in GC by targeting MYC and inhibiting cellular proliferation and invasion. All together these results suggest that these miRNAs can be used as targets for new treatment strategies against GC.

Several studies revealed that the miR-29 family (miR-29a-c) was inversely correlated with MYC expression and regulates cell growth and survival by targeting CDK6 (Cell division protein kinase 6), IGF1R (Insulin Like Growth Factor 1 Receptor), TCL1 (T-cell leukemia/lymphoma protein 1A), PI3K (Phosphoinositide 3-kinase) and MCL1 (Induced myeloid leukemia cell differentiation protein) [120–122]. However, Gong et al. found that miR-29 suppresses GC cell proliferation or invasiveness by targeting the cell cycle G1/S transition gene Cyclin D2 (CCND2) or MMP2 (matrix metallopeptidase 2), which encodes for an enzyme that degrades extracellular matrix [122]. The mechanism is unknown yet, but it is well established that MYC directly suppresses miR-29 [120,123]. As reported by Yan et al., miR-29b is recognized as an essential regulator of epithelial-mesenchymal transition (EMT) and is directly involved in cancer metastasis and chemoresistance [124]. Moreover, Saito and colleagues have reported that the selective COX2 (cyclooxygenase-2) inhibitors, as Celecoxib, inducing apoptosis, which suggests that miR-29c restoring may be a possible treatment for GC [125]. In contrast, Wang et al. found that in GC this miRNA acts as a metastatic suppressors by directly targeting catenin-δ (CTNNND1), a gene involved in cell to cell adhesion and signal transduction [126]. These discoveries suggest the differential roles for miR-29, not only acting as tumor suppressor miRNA in GC, but also serving as predictors for GC prevention.
MYC can induce mir-9-3 expression that targets E-cadherin (CDH1), a cellular adhesion protein essential for the cell-cell contact of the gastric epithelium, and promoting tumor cell migration and invasion, leading to EMT in GC [83, 127]. The MYC and N-MYC regulation of mir-9 seems to be one of the main pathways to metastasis [128, 129]. In neuroblastoma patients, N-MYC amplification directly correlates with the mir-9 levels and metastatic spread [128]. On the contrary, let-7 has target genes [HMG2A (High Mobility Group AT-Hook 2), IMP-1 (IGF2 mRNA-binding protein 1), LIN28B (Lin-28 homolog B), Ras, and MYC] important for cancer cell stemness [130]. Although let-7a expression was high in GC cell lines, it expression diminished progressively during the progression of gastric mucosa cancerization, confirming that the regulation of let-7a expression may be used as a novel biomarker and molecular mechanism of drug response to treatment [114]. Enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase involved in the silencing of many genes related to cell proliferation and differentiation. EZH2 in turn enhances H3K27 trimethylation and DNA methylation in let-7 promoter, and, as a consequence, let-7a and let-7c expressions are downregulated, resulting in Ras-ERK pathway activation [77]. Additionally, a previous mentioned study showed that GKN1 inhibits EZH2 expression through miR-185 [118]. GKN1 is considered a tumor suppressor gene as it indirectly inhibits EZH2 and DNMT1, through miR-185 and directly inhibits the Histone deacetylase 1 (HDAC1). The 8q24.21 PVT1 oncogene also regulates EZH2 activity. PVT1 recruits EZH2 to occupy the genomic sites of P15/INK4b and P16/INK4b genes, silencing these gene expressions and enforcing GC cell proliferation [34, 131]. The alteration of DNMT1 and HDAC1 expression can lead to demethylation and histone deacetylation, respectively, of several genes important for the maintenance of cell homeostasis, for example, MYC, E-cadherin, CDKN1A, and CDKN2A [132–135].

Other miRNAs such as miR-135a, miR-186, miR-494, miR-200c, miR-374a/b, miR-101 and miR-548 are also targeted by MYC gene (Table 2). mir-101 is downregulated in GC cell lines, and when overexpressed decreases MYC mRNA and protein expression and decreases cell growth, colony formation, and the number of cells in S phase, while increases the number of cells in G1 phase [99]. Similarly, miR-25 affects the control of cell cycle. Zhang et al. reported miR-25 upregulation in AGS cells playing an antiapoptotic role as it inhibited FBXW7 and promoted oncopgenes, such as MYC and cyclin E1 (CCNE1), required for G1/S transition [86]. Moreover, the expressions of CCNE1 and MYC are promoted by the upregulation of miR-25, suggesting a possible regulatory mechanism of miR-25 in AGS cells. As mentioned above, cagA enhances MYC expression, and MYC regulates EZH2 through miR-26 and miR-101 downregulation (Figure 3) [92]. The H. pylori infection also suppresses MYC-induced miR-22 expression in the gastric mucosa, and is associated with an abnormal cell proliferation [91]. miR-22 is characterized as a key regulator of the self-renewal machinery of the hematopoietic system. This miRNA acts as a proto-oncogenic miRNA via genome-wide deregulation of the epigenetic state through the inhibition of methylcytosine dioxygenase TET2 proteins [136]. On the contrary, miR-22 is suppressed by H. pylori infection, leading to uncontrolled gastric epithelial cell proliferation and overexpression of NLRP3 (NACHT, LRR and PYD domains-containing protein 3), a gene that helps the cell to recognize pathogen-associated molecular patterns [91]. These results indicate that the environment influences the modulation of miRNAs that consequently regulate important pathways of cell proliferation.

The polycistronic miRNA cluster miR-17-92 encodes six matures miRNAs (miR-17; miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92a-1), also known as oncomiR-1, and is overexpressed in GC [60]. A mice model that overexpresses the miR-17-92 cluster developed spontaneous benign tumors in the intestinal tract [88]. Interestingly, MYC functions as a transcriptional factor to miR-17-92 gene, resulting in the upregulation of this cluster and contributing to MYC oncogenic proprieties [60, 90, 137], and miR-17 overexpression is associated with MYC in GC tissues [88]. Another example of the importance of this cluster is miR-29, which is observed to be downregulated in GC, and its increased tissue expression is associated with higher overall survival rate [95]. miR-18a, miR-19a, and miR-19b are also capable of inducing MYC expression. Ectopic expression of miR-18a is capable of retarding gastric tumor growth and angiogenesis through the inhibition of mTOR pathway and is inversely correlated with PIAS3.
expression, a STAT3 inhibitor, leading to STAT3p upregulation and induction of MYC expression, with a high predictive value for prognosis of patients with GC [89,138,139]. miR-19a and miR-19b are also upregulated in GC samples, and directly target MXD1 (MAX Dimerization Protein 1), an important molecule that competes with MYC for MAX (Myc-Associated factor X) binding, impairing the oncogenic MYC-MAX-MXD1 network [140]. Therefore, miR-19a/b are linked to MYC overexpression through MXD1 inhibition. However, the complete molecular mechanism underlying miR-17-92 cluster overexpression has not been clearly evaluated in GC [88]. The robust genetic circuitries for the maintenance of cellular dysfunction in GC generate a molecular complex relationship between MYC and miRNAs. This complex relationship implies the control of MYC oncogene pathways leading to tumor development and progression. The studies herein mentioned suggest that miRNAs can not only act directly in one of the main interactions pathways that control MYC expression in GC but also have potential roles as targets for new therapeutic strategies against GC.

Finally, several miRNAs modulate the multidrug resistance of GC, and understanding their role in MYC oncopathway and in the carcinogenesis can elucidate the mechanisms responsible for low survival rate of GC patients. Cao et al. showed that miR-1284 is downregulated in GC cells, and when it is reintroduced, it enhances the drug-induced apoptosis and impairs the migration and invasion of GC cells [113]. Another example is the down-regulation of miR-135b, which was capable of multidrug-resistant protein repression and cell proliferation and induction of cell apoptotic rate of GC cells [141]. Taken together, all the above studies indicate that understanding the complex relationship between MYC and miRNAs is extremely important for gastric carcinogenesis, prognosis and treatment response.

3.3. MYC can Promote Angiogenesis through the Regulation of microRNAs

Another interesting point is that miR-15a/16-1, miR-26a, miR-29, miR-34a, and miR-150 can suppress innumerable survival signaling pathways; however, they are repressed by MYC (Figure 3) [60,84,85]. Moreover, MYC can act as a vascular endothelial growth factor (VEGF) transcriptional factor since it upregulates the expression of proangiogenic factors, promoting angiogenesis and vasculogenesis [142]. Furthermore, in silico data showed that at least eight miRNAs that strictly regulate the VEGF translation are known (miR-15a, miR-16, miR-17, miR-20a, miR-34a, miR-93, miR-106a, miR-106b], all under MYC control [143]. The VEGF is one of the most important angiogenic growth factors, therefore these results highlight the importance of the deregulation of MYC’s angiogenic properties in the microenvironment during tumors establishment and progression.

4. Conclusions

MYC and other 8q24.21 genes are associated with GC development and progression. We showed that miRNAs have an influence on the expression of MYC and vice versa. One of the major consequences of MYC activation is the extensive reprogramming of the expression pattern of miRNAs in tumor cells, which is closely linked to the modulation of critical pathways associated with cancer etiology, including MYC-MAX-MXD1 and Ras-ERK pathways. Therefore, the studies reviewed revealed that MYC and miRNAs have a very complex interaction in GC that can be affected by external factors, such as bacterial and virus infection. Despite being one of the best-known and studied oncogenes, there is a lack of understanding regarding the application of this information for therapeutic interventions against GC. This application should likely be studied in conjunction with miRNAs expression and action once they appear to be highly correlated. Thus, the investigation of the role of miRNAs helps in the elucidation of underlying mechanisms of gastric carcinogenesis and are potential biomarkers that monitor the alteration of critical genomic driver regions, targeting new treatment strategies against GC.

In fact, besides acting as tumor biomarkers, the miRNAs mentioned in this review may also be used as targets for cancer therapies. Furthermore, there are some examples of miRNA-based therapies currently on clinical trials. A quick search on clinicaltrials.org using the key words “miR” and “cancer” reveals that there are 334 studies and many of them are active. For example, the biotechnology company
miRagen has been developing therapies using miRNAs: MRG-110, MRG-106 and MRG-201. The first one, MRG-110, uses an LNA-modified antisense oligonucleotides to inhibit miR-92 and works by increasing the growth of new blood vessels to treat wound healing and heart failure. MRG-106 uses the same technology to silence miR-155 to treat T-cell lymphoma. MRG-201, in contrast, mimics miR-29 to treat pathological fibrosis, such as keloids and scar tissue formation. Developed by Regulus Therapeutics, RGLS5579 and RG-012 are design to treat patients with glioblastoma multiforme (GBM) and Alport Syndrome, respectively. These drugs target miR-10b and miR-21 inhibiting their function. In addition, there are other less explored approaches, such as using CRISPRi (CRISPR interference) to silence the expression of upregulated miRNAs. In this strategy, a dead-Cas9 fused with transcriptional repressors is targeted to the promoter region of a miRNA, preventing its expression [144,145]. Although there are therapies showing promising results, one of the main challenges in these approaches is to find efficient delivery methods [146]. In this context, a few options are currently being tested, for instance intratumoral injections [147], viral vectors [148], lipid vectors [149], and inorganic nanoparticles [150].

To our knowledge, there are no clinical trials using miRNAs as therapeutic targets for GC to date. Therefore, the characterization of these molecules will be useful in the development of new prognosis, diagnosis, and treatment strategies for patients with GC.

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**Abbreviations**

- **GC** Gastric cancer
- **miRNA** microRNA
- **RISC** RNA-induced silencing complex
- **H. pylori** Helicobacter pylori
- **IARC** International Agency for Research on Cancer
- **EMT** Epithelial-mesenchymal matrix
- **GBM** Glioblastoma multiforme
- **CRISPRi** CRISPR interference

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