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The role of microRNAs in *Helicobacter pylori* pathogenesis and gastric carcinogenesis

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Gastric carcinogenesis is a multistep process orchestrated by aberrancies in the genetic and epigenetic regulation of oncogenes and tumor suppressor genes. Chronic infection with *Helicobacter pylori* is the strongest known risk factor for the development of gastric cancer. *H. pylori* expresses a spectrum of virulence factors that dysregulate host intracellular signaling pathways that lower the threshold for neoplastic transformation. In addition to bacterial determinants, numerous host and environmental factors increase the risk of gastric carcinogenesis. Recent discoveries have shed new light on the involvement of microRNAs (miRNAs) in gastric carcinogenesis. miRNAs represent an abundant class of small, non-coding RNAs involved in global post-transcriptional regulation and, consequently, play an integral role at multiple steps in carcinogenesis, including cell cycle progression, proliferation, apoptosis, invasion, and metastasis. Expression levels of miRNAs are frequently altered in malignancies, where they function as either oncogenic miRNAs or tumor suppressor miRNAs. This review focuses on miRNAs dysregulated by *H. pylori* and potential etiologic roles they play in *H. pylori*-mediated gastric carcinogenesis.

Keywords: gastric cancer, *Helicobacter pylori*, microRNA, cell cycle, proliferation, apoptosis

INTRODUCTION

Microbial infections are among the most significant causes of cancer worldwide with nearly one in five malignancies resulting from infectious agents (Parkin, 2006). Gastrointestinal cancers represent a major global health concern and account for nearly 20% of all cancer-related deaths (Ferlay et al., 2007). Despite the decreasing incidence of gastric cancer in developed countries, it remains the second leading cause of cancer-related death throughout the world, with ∼700,000 deaths attributed to this malignancy annually (Parkin et al., 2005). The major contributing factor to the development of gastric cancer is colonization and chronic infection by the bacterial pathogen, *Helicobacter pylori*. *H. pylori* selectively colonizes the gastric epithelium of over 50% of the world's population and typically persists for the lifetime of the host. Among colonized individuals, however, only a fraction develop gastric adenocarcinoma, emphasizing the importance of understanding the pathogenic mechanisms by which *H. pylori* promotes chronic inflammation and the progression to gastric cancer.

VIRULENCE FACTORS THAT MEDIATE *HELICOBACTER PYLORI* PATHOGENESIS

Chronic gastric inflammation induced by the bacterial pathogen, *H. pylori*, is the strongest known risk factor for the development of atrophic gastritis, metaplasia, dysplasia, and ultimately gastric adenocarcinoma (**Figure 1**). *H. pylori* is a Gram-negative, helical-shaped bacterium specifically adapted to persist within the human gastric niche. *H. pylori* possesses numerous elements to successfully colonize the gastric mucosa, establish chronic infection, and induce gastric pathology. *In vivo*, approximately 20% of *H. pylori* adhere to the gastric epithelium (Hessey et al., 1990). The large repertoire of adhesins expressed by *H. pylori* likely contribute to its specific adaptation to the gastric niche, allowing flexibility to target specific host cells and to exert a dynamic range of effector functions on host cells. *H. pylori* expresses a number of adhesins that have been linked to virulence. SabA (sialic acid-binding adhesin), which binds host sialyl-Lewis^x, contributes to *H. pylori* persistence and mediates chronic gastric inflammation and injury (Mahdavi et al., 2002). The presence of blood group antigen-binding adhesin (BabA), which binds the host Lewis^b blood group antigen, increases the risk of gastric cancer in a synergistic fashion with other virulence factors, such as CagA (Ilver et al., 1998; Gerhard et al., 1999).

Following adherence and colonization of the gastric mucosa, *H. pylori* induces chronic gastritis and gastric injury, which are characterized by both neutrophilic and lymphocytic inflammation (Marshall et al., 1985; Goodwin et al., 1986). *H. pylori* expresses a number of factors capable of modulating the host immune system and eliciting proinflammatory immune responses. Some of these virulence factors include vacuolating cytotoxin (VacA) and the *cag* (cytotoxin associated gene) pathogenicity island. VacA is coded by the gene *vacA*, which is present in all strains of *H. pylori*, and which exhibits vacuolating activity (Leunk et al., 1988; Cover and Blaser, 1992; Cover et al., 1994; Phadnis et al., 1994; Schmitt and Haas, 1994; Telford et al., 1994). Additionally, VacA can induce apoptosis of host cells (Kuck et al., 2001; Xia and Talley, 2001) and suppress proliferation of T and B lymphocytes (Boncristiano et al., 2003; Gebert et al., 2003; Sundrud et al., 2004), which may contribute to the persistence of *H. pylori* through dysregulation of the host immune response. The *cag* pathogenicity island is present in

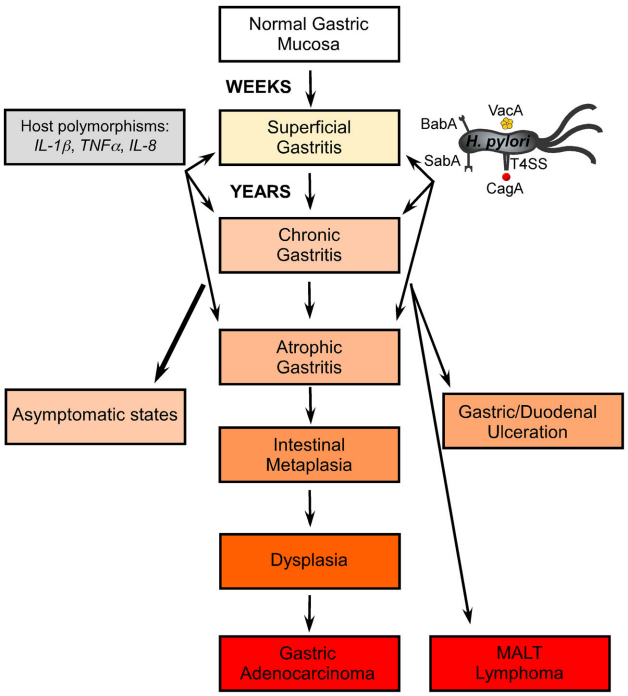

FIGURE 1 | Progression to gastric adenocarcinoma. *H. pylori* colonizes the human gastric mucosa and causes superficial gastritis and chronic inflammation over weeks to months. *H. pylori* expressing key virulence factors, such as the *cag* type 4 secretion system (T4SS), and host genetic polymorphisms in *IL-1β*, *TNFα*, and *IL-8* promoters that promote high expression of proinflammatory cytokines, augment the risk for developing atrophic gastritis, intestinal metaplasia, dysplasia, and ultimately, gastric adenocarcinoma.

∼60% of all *H. pylori* strains and its presence is strongly associated with an increased risk of severe gastritis, ulcer disease, and gastric cancer (Censini et al., 1996; Tomb et al., 1997; Akopyants et al., 1998; Alm et al., 1999). The *cag* island encodes a type 4 secretion system (T4SS), which injects effector molecules, such as CagA, into host cells. CagA is a 120- to 140-kD protein that contains a number of tyrosine phosphorylation motifs (Covacci et al., 1993; Tummuru et al., 1993). Following its injection into host cells, CagA exerts a wide range of phosphorylation-dependent and independent effects, such as cytoskeletal rearrangements, disruption of cell polarity, and mitogenic and proinflammatory responses (Polk and Peek, 2010). Cumulatively, these bacterial factors contribute to adherence, persistence, host immune modulation, and virulence of *H. pylori* within the gastric niche, ultimately resulting in *H. pylori*-mediated chronic inflammation and a series of pathological outcomes that facilitate the development of gastric cancer.

HOST FACTORS THAT CONTRIBUTE TO GASTRIC CARCINOGENESIS

In addition to microbial factors that potentiate gastric disease, there are a number of host factors that contribute to chronic gastritis and the progression to gastric adenocarcinoma. Cyclooxygenases (COX) are key enzymes that catalyze prostaglandin synthesis. Of the three isoforms identified, COX-2 is upregulated in gastric epithelial cells upon co-culture with *H. pylori* (Romano et al., 1998; Juttner et al., 2003; Meyer et al., 2003; Wu et al., 2005) and within the gastric mucosa of *H. pylori*-infected individuals (Sawaoka et al., 1998; Fu et al., 1999; McCarthy et al., 1999). *In vivo* studies show that COX-2 is further upregulated in *H. pylori*-mediated adenocarcinoma (Ristimaki et al., 1997; Sung et al., 2000). COX-2 expression levels are considered an independent factor for poor prognosis and correlate with reduced patient survival, suggesting that *H. pylori*-induced COX-2 overexpression is a risk factor for the development of gastric cancer.

Other host factors that increase the propensity for chronic inflammation and gastric adenocarcinoma are polymorphisms within human *IL-1*β (interleukin-1), *TNF*-α (tumor necrosis factor), and *IL-8* promoters (El-Omar et al., 2000, 2003; Machado et al., 2001; Furuta et al., 2002), which lead to increased expression of the proinflammatory cytokines IL-1β, TNF-α, and IL-8 (**Figure 1**). These polymorphisms in combination with *H. pylori* virulent genotypes increase the risk of gastric cancer up to 87-fold over baseline (Figueiredo et al., 2002), emphasizing the importance of microbial–host interactions in the development of gastric cancer. Collectively, data demonstrate that *H. pylori* virulence factors, host genetics, and environmental factors interact to induce and maintain the persistent inflammatory immune response that initiates the multistep process leading to gastric cancer.

microRNAs

Recent discoveries have shed new light on the involvement of host microRNAs (miRNAs) in gastric carcinogenesis. miRNAs are small, non-coding RNAs ∼20–25 nucleotides in length, which function as critical post-transcriptional regulators of gene expression (Bartel, 2009). miRNAs were first characterized in 1993 (Lee et al., 1993), but their distinct role in transcriptional regulation was not recognized until the early 2000s. Most miRNAs are found in intergenic regions and contain their own promoter and regulatory units. Processed miRNAs function by binding to the 3′ untranslated region (3′UTR) of messenger RNAs (mRNAs), typically resulting in mRNA degradation and gene silencing or translational repression (Bartel, 2009). It is estimated that the human genome encodes thousands of miRNAs, targeting ∼30–60% of all protein-coding genes (Lewis et al., 2003). miRNAs are involved in many biological processes, including development, differentiation, angiogenesis, cell cycle progression, proliferation, apoptosis, and signal transduction pathways (Ambros, 2004). Dysregulation of miRNA expression with subsequent disruption of these biological processes can result in disease states. There is an increasing body of evidence regarding the regulatory roles of miRNAs in immune and inflammatory disorders (Wu et al., 2008; Sonkoly and Pivarcsi, 2009), and aberrant expression of miRNAs is observed in many cancers (Lu et al., 2005; Volinia et al., 2006). Thus, recent studies have begun to dissect the mechanisms by which miRNAs function as either oncogenic miRNAs (oncomiRs) or tumor suppressors to promote or prevent tumorigenesis.

DYSREGULATION OF miRNAs IN *H. PYLORI*-INDUCED GASTRIC CARCINOGENESIS

The number of studies analyzing miRNA expression profiles in gastric cancer is rapidly increasing and a comprehensive list of

miRNAs dysregulated in gastric cancer, confirmed mRNA targets, and the biological processes affected is shown in **Tables A1** and **A2** in the Appendix. The first study to address miRNA expression profiles in various cancers, including gastric cancer, was performed in 2005 (Lu et al., 2005). Subsequent studies have not only focused on miRNA expression profiles in gastric cancer, but also those that are altered in response to *H. pylori*.

Matsushima et al. (2011) conducted a study to characterize miRNA expression signatures in *H. pylori*-infected human gastric mucosa. Using high throughput profiling analysis, 31 miRNAs were identified as being differentially expressed between *H. pylori*-infected and *H. pylori*-uninfected gastric mucosa. The relationship between miRNA expression levels and *H. pylori*-induced acute inflammation, characterized by neutrophil infiltration, and chronic inflammation, characterized by mononuclear cell infiltration were also determined. Expression levels of many miRNAs correlated with either the degree of acute or chronic inflammation and in some cases both (**Tables 1** and **2**). The relationship between miRNA expression and extent of glandular atrophy, and intestinal metaplasia was also assessed, but no significant correlations were found (Matsushima et al., 2011). A comprehensive list of miRNAs dysregulated by *H. pylori*, confirmed mRNA targets, and biological processes affected is shown in **Tables 1** and **2**. These data suggest that *H. pylori* infection affects global miRNA expression in human gastric mucosa, and this effect is, in part, linked to *H. pylori*-induced host inflammatory immune responses.

miRNAs that are dysregulated in response to *H. pylori* infection may not be the same miRNAs that are dysregulated in later stages of gastric disease. A comprehensive review of the literature, however, revealed that there is a select subset of miRNAs dysregulated both following *H. pylori* infection as well asin gastric cancer. These include downregulated miRNAs, *let-7a*, *miR-31*, *miR-101*, *miR-141*, *miR-203*, *miR-210*, *miR-218*, *miR-375*, and *miR-449* as well as upregulated miRNAs, *miR-17*, *miR-20a*, *miR-21*, *miR-146a*, *miR-155*, and *miR-223*. These miRNAs may be more biologically relevant to *H. pylori*-induced gastric inflammation and carcinogenesis and represent fruitful targets for studies focused on cancer that develops in the context of *H. pylori* infection.

The next sections will discuss miRNA dysregulation in *H. pylori*-induced disease and how specific miRNAs control various biological processes related to (1) host inflammatory immune response, (2) cell cycle progression, and (3) apoptosis and proliferation.

HELICOBACTER PYLORI-INDUCED miRNA DYSREGULATION TO CONTROL HOST INFLAMMATORY RESPONSES

Host cells recognize invading pathogens and/or pathogen-associated molecular patterns (PAMPs) through membrane-associated or cytoplasmic pathogen recognition molecules known as Toll-like receptors (TLRs) and Nod-like receptors (NLRs), respectively. PAMPs activate adaptor proteins and transcription factors that mediate host innate immunity through activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling (**Figure 2**). Gastric epithelial cells are the initial host element encountered by *H. pylori*. The innate immune response induced in epithelial cells is characterized by NOD1-dependent activation of NF-κB in response to *H. pylori* peptidoglycan (PGN), which is injected into host cells via the *cag* T4SS (Viala et al., 2004). Activation of NF-κB by *H. pylori* leads to induction of the proinflammatory cytokine IL-8 and likely contributes to carcinogenesis through activation of downstream targets that mediate inflammation, cell cycle progression, proliferation, and apoptosis. Myeloid cells constitute a second line of defense and secrete proinflammatory cytokines such as IL-6, IL-1, and TNF-α to establish T and B lymphocyte-mediated adaptive immunity.

The involvement of miRNAs in modulating both the innate and adaptive immune responses is well established (Chen et al., 2004) and *H. pylori* can dysregulate miRNA expression to evade host defenses and successfully persist in the gastric niche. *miR-146a* and *miR-155* are specifically involved in *H. pylori*-induced negative regulation of the proinflammatory immune response (**Figure 2**). Changes in *miR-146a* expression occur in the development of gastric cancer and in the negative regulation of the innate inflammatory immune response. Single-nucleotide polymorphisms (SNPs) in *miR-146a* are associated with an increased susceptibility to gastric cancer (Okubo et al., 2010) and *H. pylori* upregulates *miR-146a in vitro* and *in vivo* in a CagA-independent and an NF-κB-dependent manner (Liu et al., 2010; Li et al., 2011a). *miR-146a* targets the TLR-signaling adaptor molecules *IRAK1* (interleukin-1 receptor-associated kinase) and *TRAF6* (TNF receptor-associated factor), resulting in negative regulation of TLR and downstream proinflammatory signaling (**Figure 2**; Liu et al., 2010; Li et al., 2011a). As a result, *miR-146a* overexpression negatively regulates *H. pylori*-induced IL-8, TNF-α, IL-1β, GRO-α [CXCL1, chemokine (C-X-C motif) ligand], and MIP-3α (macrophage inflammatory protein) expression, all key components to the proinflammatory innate and adaptive immune responses (Liu et al., 2010; Li et al., 2011a).

The second miRNA involved in *H. pylori*-induced downregulation of the host inflammatory immune response, *miR-155*, plays a critical role in regulating lymphocyte homeostasis and tolerance (Thai et al., 2007). *miR-155* is increased in many malignancies of B cell or myeloid origin (Volinia et al., 2006). In transgenic murine models of *miR-155* overexpression, mice develop spontaneous B cell lymphomas (Costinean et al., 2006). *miR-155* is induced during both bacterial and viral infections in myeloid cells through activation of TLR-signaling pathways. *H. pylori* upregulates *miR-155* expression *in vitro* and *in vivo*, which occurs in an NF-κB-dependent manner, and ultimately results in decreased induction of the proinflammatory cytokines, IL-8, and GRO-α (Xiao et al., 2009b; Tang et al., 2010). *miR-155* targets *MyD88* (myeloid differentiation primary response gene), the universal adapter protein used by TLRs to activate NF-κB (**Figure 2**; Xiao et al., 2009b; Tang et al., 2010). Decreased levels of MyD88 subsequently result in decreased NF-κB activation and dampening of the host inflammatory response (Xiao et al., 2009b; Tang et al., 2010). Therefore, these data demonstrate that *H. pylori* dysregulates host miRNA expression to manipulate the host inflammatory immune response, which may promote bacterial survival and persistence within the gastric mucosa. Because these miRNAs have established roles in carcinogenesis as well as innate immunity, they could serve as an important link between *H. pylori*-induced inflammation and carcinogenesis.

Table 1 | miRNAs downregulated in response to *H. pylori*.

miRNAs	Target mRNAs	Biological process targeted	Reference
let-7a+	***RAB40C***	**Cell cycle progression**	Matsushima et al. (2011), Motoyama et al. (2008), Yang et al. (2011)
		Proliferation	
	HMGA2	**Invasion**	
*let-7b**	*HMGA2*	Invasion	Matsushima et al. (2011), Motoyama et al. (2008)
let-7d	*HMGA2*	Invasion	Matsushima et al. (2011), Motoyama et al. (2008)
let-7e	*HMGA2*	Invasion	Matsushima et al. (2011), Motoyama et al. (2008)
let-7f	*HMGA2*	Invasion	Matsushima et al. (2011), Motoyama et al. (2008)
miR-1	ND	Proliferation	Saito et al. (2011)
miR-31+	**ND**	**ND**	Matsushima et al. (2011)
miR-32	ND	ND	Matsushima et al. (2011)
miR-34b	ND	ND	Suzuki et al. (2010)
miR-34c	ND	ND	Suzuki et al. (2010)
miR-101	***COX-2***, ***FOS***	**Proliferation**	Matsushima et al. (2011), Varambally et al. (2008), Wang et al. (2010)
	MCL1	**Apoptosis**	
	EZH2	**Invasion migration**	
miR-103#	ND	ND	Matsushima et al. (2011)
miR-106b	*p21*	Cell cycle progression	Kan et al. (2009), Matsushima et al. (2011), Petrocca et al. (2008)
		Proliferation	
	BIM	Apoptosis	
miR-125a	*ERBB2*	Proliferation	Matsushima et al. (2011), Nishida et al. (2011)
miR-130a	ND	ND	Matsushima et al. (2011)
miR-133	ND	Proliferation	Saito et al. (2011)
miR-141#	***FGFR2***	**Proliferation**	Du et al. (2009), Matsushima et al. (2011)
miR-200a+	*ZEB1, ZEB2*	Epithelial to mesenchymal transition (EMT)	Ahn et al. (2011), Matsushima et al. (2011), Shinozaki et al. (2010)
miR-200b+	*BCL2, XIAP*	Apoptosis	Ahn et al. (2011), Matsushima et al. (2011), Shinozaki et al. (2010),
	ZEB1, ZEB2	EMT	Zhu et al. (2011a)
miR-200c+	*BCL2, XIAP*	Apoptosis	Matsushima et al. (2011), Shinozaki et al. (2010), Zhu et al. (2011a)
		EMT	
miR-203	***ABL1***	**Proliferation**	Craig et al. (2011b), Matsushima et al. (2011)
		Invasion	
miR-204	*EZR*	Proliferation	Lam et al. (2011), Matsushima et al. (2011)
miR-210	**ND**	**ND**	Matsushima et al. (2011)
miR-214	ND	ND	Matsushima et al. (2011)
miR-218	***ECOP***	**Proliferation**	Gao et al. (2010), Tie et al. (2010)
		Apoptosis	
	ROBO1	**Invasion and metastasis**	
miR-320+	ND	ND	Matsushima et al. (2011)
miR-372	*LATS2*	Cell cycle progression	Belair et al. (2011)
miR-373	*LATS2*	Cell cycle progression	Belair et al. (2011)
miR-375+	***PDK1***, ***14-3-3***	**Apoptosis**	Ding et al. (2010), Matsushima et al. (2011), Tsukamoto et al. (2010)
	JAK2	**Proliferation**	
miR-377	ND	ND	Matsushima et al. (2011)
miR-379	ND	ND	Matsushima et al. (2011)
miR-429+	*BCL2, XIAP*	Apoptosis	Matsushima et al. (2011), Sun et al. (2011), Zhu et al. (2011a)
	MYC	Proliferation	
miR-449	***GMNN***, ***CCNE2***	**Cell cycle progression**	Bou Kheir et al. (2011), Lize et al. (2011)
	MET, ***SIRT1***	**Proliferation**	
miR-455	ND	ND	Matsushima et al. (2011)
miR-491-5p	ND	ND	Matsushima et al. (2011)
miR-500	ND	ND	Matsushima et al. (2011)

(Continued)

Table 1 | Continued

miRNAs	Target mRNAs	Biological process targeted	Reference
miR-532#	ND	ND	Matsushima et al. (2011)
miR-652#	ND	ND	Matsushima et al. (2011)

*Target criteria included (1) reduced protein expression upon miRNA transfection in gastric cells or expression inversely correlated with miRNA in gastric tissue or (2) presence of miRNA binding site on the 3′ UTR of target mRNA confirmed by luciferase reporter assay. ND, target mRNA or biological process not determined. *, miRNA expression correlates with acute inflammation. #, miRNA expression correlates with chronic inflammation. +, miRNA expression correlates with both acute and chronic inflammation. Bold indicates miRNA also downregulated in gastric cancer.*

Table 2 | miRNAs upregulated in response to *H. pylori* infection.

miRNAs	Target mRNAs	Biological process targeted	Reference
miR-17^	***p21***	**Cell cycle progression**	Saito et al. (2010)
miR-20a^	***p21***	**Cell cycle progression**	Saito et al. (2010)
miR-21	***PDCD4***	**Proliferation**	Zhang et al. (2008)
	RECK	**Apoptosis**	
	PTEN	**Invasion**	
miR-146a	***IRAK1, TRAF6***	**Immune response**	Li et al. (2011a), Liu et al. (2010), Xiao et al. (2011)
		Proliferation	
	SMAD4	**Apoptosis**	
miR-155	***IKK-ε, SMAD2***	**Immune response**	Fassi Fehri et al. (2010), Oertli et al. (2011), Tang et al. (2010), Xiao et al. (2009b)
	FADD, PKIα	**Apoptosis**	
miR-223*	***EPB41L3***	**Invasion and metastasis**	Li et al. (2011b), Matsushima et al. (2011)

*Target criteria included (1) reduced protein expression upon miRNA transfection in gastric cells or expression inversely correlated with miRNA in gastric tissue or (2) presence of miRNA binding site on the 3′ UTR of target mRNA confirmed by luciferase reporter assay. ND, target mRNA or biological process not determined. ^, miRNA expression induced by CagA overexpression, not H. pylori infection (Saito et al., 2010). *, miRNA expression correlates with acute inflammation. Bold indicates miRNA also upregulated in gastric cancer.*

HELICOBACTER PYLORI AND miRNAS REGULATE CELL CYCLE PROGRESSION

Disruption of cell cycle progression and increased cellular proliferation are common features of malignancies. Cell cycle progression requires coordinated expression of cyclins, which results in sequential activation of cyclin-dependent kinases (CDKs). miRNA dysregulation promotes cell cycle progression by upregulating cyclin expression and/or downregulating expression of CDK inhibitors (p15, p16, p18, p19, p21, p27, p28, p57) in various cancers, including gastric cancer (**Figure 3**). *miR-449*, a miRNA downregulated in *H. pylori*-infected gastric tissue and in gastric cancer, targets *GMNN* (geminin) and *CCNE2* (cyclin E2; **Figure 3**). Both geminin and cyclin E2 are overexpressed in numerous malignancies and promote M/G1 and G1/Scell cycle progression and cell proliferation (Bou Kheir et al., 2011; Lize et al., 2011). Consequently, downregulation of *miR-449*, as occurs following *H. pylori* infection, promotes cell cycle progression and proliferation through upregulation of geminin and cyclin E2.

p42.3, a recently identified protein significantly upregulated in gastric cancer, regulates G2/M cell cycle progression and proliferation in gastric cancer cells (Xu et al., 2007). *miR-29a*, a miRNA significantly downregulated in gastric cancer, targets *p42.3* (Cui et al., 2011; **Figure 3**). Thus, the downregulation of *miR-29a* results in a reciprocal increase in p42.3 expression, promoting increased cell cycle progression and proliferation.

The retinoblastoma protein (RB1) is a tumor suppressor dysregulated in many cancers. RB1 functions to prevent excessive cell proliferation by inhibiting G1/S cell cycle progression. RB1 binds and inhibits transcription factors of the E2F family. When RB1 is bound to E2F the complex acts as a growth suppressor and prevents progression through cell cycle. A number of miRNAs target these factors. For instance, *miR-106a* is upregulated in gastric cancer and targets *RB1* (Volinia et al., 2006), while *miR-331-3p* is downregulated in gastric cancer and targets *E2F1* (Guo et al., 2010; **Figure 3**).

TGFβ suppresses gastric cancer cell proliferation via the transcriptional upregulation of the CDK inhibitor, *p21* (Yoo et al., 1999). *miR-93* and *miR-106b* directly target *p21*, resulting in its transcriptional silencing and impairment of the tumor-suppressing activity of TGFβ (Petrocca et al., 2008; Kan et al., 2009; **Figure 3**). In addition, *miR-25* targets the CDK inhibitor, *p57*, while *miR-221* and *miR-222* target the CDK inhibitors, *p27* and *p57* (Kim et al., 2009; **Figure 3**). These oncogenic miRNA clusters are also significantly upregulated in gastric cancer (Volinia et al., 2006; Petrocca et al., 2008; Guo et al., 2009; Kim et al., 2009; Yao et al., 2009). Overexpression of most of these miRNAs results in activation of CDK2, thereby promoting G1/S phase progression. Since numerous reports have described the role of *H. pylori* in the modulation of cyclins, CDKs, and CDK inhibitors and their link to gastric carcinogenesis (Shirin et al., 2001), these

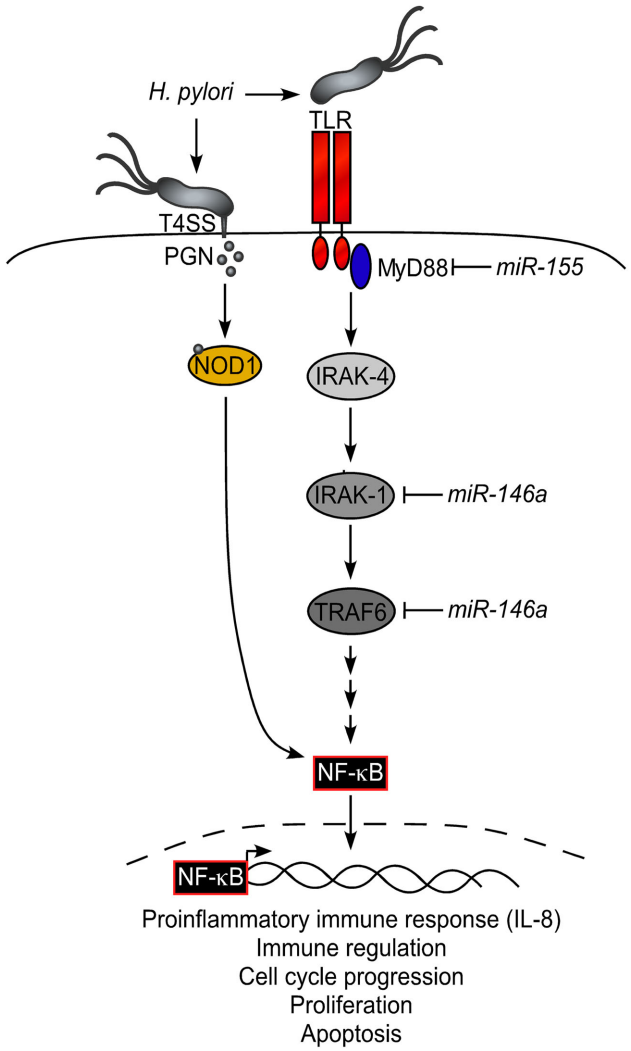

FIGURE 2 | TLR, NOD, and the NF-κB signaling pathways. Host cells recognize invading pathogens through extracellular Toll-like receptors (TLRs) and intracellular Nod-like receptors (NOD). Pathogens, such as *H. pylori*, activate TLRs and adaptor molecules that ultimately lead to NF-κB activation and a proinflammatory immune response. The key adaptor molecule responsible for signaling by TLRs is MyD88. MyD88 and other adaptor proteins (IRAK-1 and TRAF6) in this signaling cascade are targeted by miRNAs to dampen the host immune response.

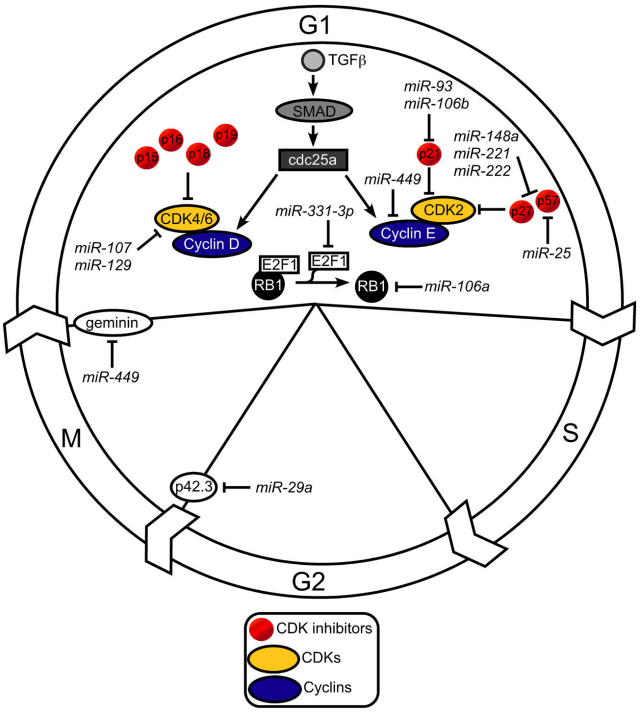

FIGURE 3 | Regulation of cell cycle progression. The cell cycle consists of four distinct phases: G1, S, G2, and M. Two key classes of regulatory molecules, cyclins and cyclin-dependent kinases (CDKs), determine a cells progress through the cell cycle. CDK inhibitors prevent the progression of cell cycle and function as tumor suppressors. miRNAs target the key regulatory molecules, cyclins and CDKs, as well as CDK inhibitors to disrupt normal cell cycle progression.

data suggest that *H. pylori* modulates expression of cyclins, CDKs, and CDK inhibitors through dysregulation of host miRNAs, which may increase the propensity for gastric transformation.

HELICOBACTER PYLORI AND miRNA DYSREGULATION INHIBIT APOPTOSIS AND PROMOTE CELL SURVIVAL

Increased cellular proliferation and evasion of apoptosis are hallmarks of cellular transformation. Apoptosis can be classified as being dependent on either the intrinsic or extrinsic pathways. The intrinsic pathway is initiated within cells and hinges on the balance of activity between pro-apoptotic and anti-apoptotic members of the Bcl-2 (B cell lymphoma 2) superfamily of proteins, which act to regulate the permeability of the mitochondrial membrane. miRNAs regulate apoptosis by altering expression and balance of members of the pro-apoptotic (e.g., Bax, Bak, Bim, Bad, Bid, and BNIP3L) and anti-apoptotic (e.g., Bcl-2, Bcl-xL, and Mcl-1) Bcl-2 protein family (**Figure 4**).

Numerous miRNAs overexpressed in gastric cancer function as oncomiRs by targeting members of the pro-apoptotic Bcl-2 protein family. In addition to their role in regulating cell cycle progression, *miR-25*, *miR-93*, and *miR-106b* also inhibit apoptosis by preventing expression of the pro-apoptotic protein, Bim (Kan et al., 2009; **Figure 4**). Overexpression of *miR-130b* also contributes to suppression of Bim and apoptosis by targeting *RUNX3* (runt-related transcription factor; Lai et al., 2010), a known tumor suppressor frequently silenced in gastric cancer (Li et al., 2002). *miR-150* targets the *EGR2* (early growth response protein; Wu et al., 2010), a tumor-suppressive transcription factor that induces apoptosis by direct transactivation of pro-apoptotic factors, Bak, and BNIP3L (Unoki and Nakamura, 2003).

Numerous tumor suppressor miRNAs target members of the anti-apoptotic Bcl-2 protein family and are consequently downregulated in gastric cancer. *miR-15b*, *miR-16*, *miR-34*, *miR-181b*, *miR-181c*, and *miR-497* directly target anti-apoptotic *BCL2* (Ji et al., 2008; Xia et al., 2008; Zhu et al., 2010b, 2011b; **Figure 4**). These miRNA clusters are downregulated in gastric cancer cells

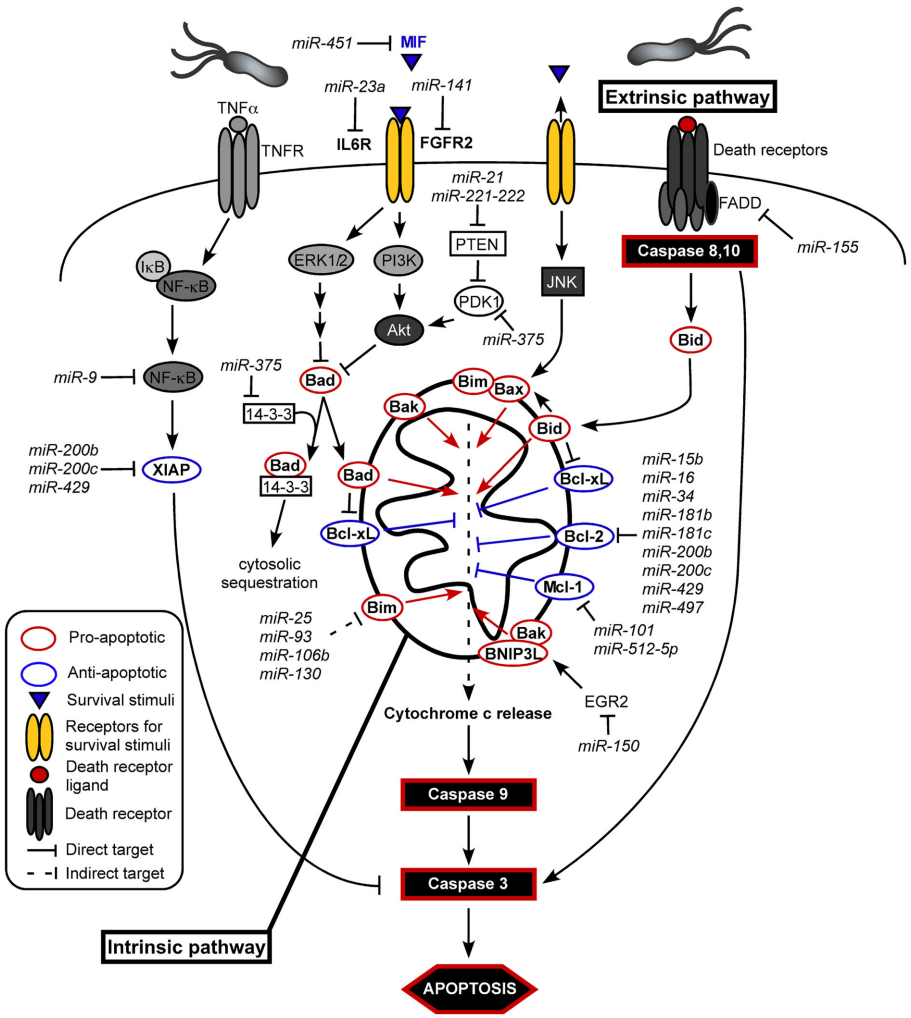

FIGURE 4 | Signaling cascades that regulate the intrinsic and extrinsic pathways of apoptosis. TNFα signaling leads to activation of NF-κB and the anti-apoptotic protein XIAP. Other receptors that detect survival factors, such as growth factors and cytokines, induce ERK1/2 and PI3K/Akt signaling cascades that ultimately result in the inhibition of the pro-apoptotic protein, Bad. In contrast, upon removal of survival factors, these receptors can signal via JNK to induce the pro-apoptotic protein, Bax. Pro-apoptotic and anti-apoptotic proteins govern the intrinsic pathway of cell death, which results in the release of cytochrome c from the mitochondria and induction of the caspase cascade. Signaling through death receptors initiate the extrinsic pathway of apoptosis, leading to the induction of caspases and cell death. There are numerous miRNAs that regulate each of these pathways and dysregulation of these miRNAs can lead to anti-apoptotic and tumorigenic responses.

(Guo et al., 2009), leading to increased expression of Bcl-2 and inhibition of apoptosis. The *miR-200bc/429* cluster is downregulated in gastric cells, and these miRNAs directly target *BCL2* and *XIAP* (x-linked inhibitor of apoptosis), leading to reduced expression and increased apoptosis (Zhu et al., 2011a; **Figure 4**). *miR-101* and *miR-512-5p* target another anti-apoptotic member of the Bcl-2 family, *MCL1* (myeloid leukemia cell differentiation protein; Saito et al., 2009; Wang et al., 2010; **Figure 4**). Both *miR-101* and *miR-512-5p* are downregulated in gastric cancer, leading to increased levels of Mcl-1 and an anti-apoptotic phenotype. In addition, *miR-101* is downregulated by *H. pylori* (Matsushima et al., 2011). *miR-449* is also likely involved in mediating the intrinsic pathway of apoptosis and has been classified as a potent inducer of cell cycle arrest and cell death. *miR-449* expression is reduced in *H. pylori*-infected gastric tissue, and its expression is lost in gastric tumors (Bou Kheir et al., 2011; Lize et al., 2011). Conversely, overexpression of *miR-449* inhibits cellular proliferation and induces significant levels of apoptosis, and since *miR-449* belongs to the family of p53-responsive miRNAs, its overexpression also results in activation of p53 and apoptosis-specific marker, caspase 3.

In contrast to the intrinsic pathway, the extrinsic pathway of apoptosis is initiated on the cell surface through the activation of specific pro-apoptotic, death receptors. Specific pro-apoptotic ligands are known to activate the extrinsic pathway of apoptosis via specific receptor binding. Ligand binding induces receptor clustering and the recruitment of the adaptor protein Fas-associated death domain (FADD), leading to induction of caspases and ultimately cell death. In addition to its role in regulating the host

immune response, *miR-155* targets *FADD* (**Figure 4**), leading to decreased expression of this key adaptor molecule (Xiao et al., 2009b). Therefore, the upregulation of *miR-155* by *H. pylori* and during carcinogenesis results in downregulation of FADD and inhibition of apoptosis.

In addition to targeting proteins directly involved in the intrinsic and extrinsic pathways of cell death, miRNAs target other factors that ultimately lead to inhibition of apoptosis and increased proliferation. *miR-375* targets 14-3-3 zeta, an anti-apoptotic protein that mediates cell survival by binding the pro-apoptotic protein Bad and sequestering it to the cytosol (Tsukamoto et al., 2010; **Figure 4**). *miR-375* also targets *PDK1* (3-phosphoinositide dependent protein kinase), a kinase that directly phosphorylates Akt, thereby regulating the PI3K/Akt signaling pathway (**Figure 4**). Overexpression of *miR-375* was shown to substantially reduce cell viability through induction of the caspase-dependent apoptotic pathway. *miR-375* is one of the most highly downregulated miRNAs in gastric cancer (Tsukamoto et al., 2010), suggesting its role as a potent tumor suppressor that contributes to the development of gastric carcinoma.

In contrast, *miR-21*, a known oncomir that targets many known tumor suppressors, is consistently upregulated in various human cancers, including gastric cancer (Volinia et al., 2006; Chan et al., 2008; Petrocca et al., 2008; Zhang et al., 2008; Guo et al., 2009), and *miR-21* expression is increased in *H. pylori*-infected gastric tissues (Zhang et al., 2008). Overexpression of *miR-21* shifts the balance between proliferation and apoptosis, increasing cellular proliferation and inhibiting apoptosis. Specifically, *miR-21* targets *PTEN* (phosphatase and tensin homolog), a tumor suppressor and negative regulator of the PI3K/Akt signaling pathway (Yamanaka et al., 2009), which is involved in both apoptotic and proliferative pathways (**Figure 4**). Mutations in *PTEN* are important in the progression of many cancers, including gastric carcinoma (Kang et al., 2002). *miR-21* likely also contributes to apoptosis by targeting *PDCD4* (programmed cell death protein 4), which is localized to the nucleus of proliferating cells; however, its direct role in apoptosis has not been elucidated (Lu et al., 2008; Motoyama et al., 2010).

Similar to PI3K/Akt signaling, the NF-κB signaling pathway is important in inhibition of apoptosis and cell survival. The NF-κB signaling cascade is activated during *H. pylori*-induced gastritis and is constitutively active in gastric cancer (Sasaki et al., 2001). *miR-218* expression is reduced in numerous cancers, including gastric cancer. *H. pylori* infection also reduces the expression of *miR-218 in vitro* and *in vivo*. *miR-218* induces apoptosis in gastric cancer cells through direct targeting of *ECOP* (epidermal growth factor receptor-co-amplified and overexpressed protein), a known positive regulator of NF-κB transcriptional activity. Downregulation of *miR-218* leads to overexpression of ECOP, inhibition of NF-κB transcriptional activation, and transcription of a downstream target COX-2, ultimately inhibiting apoptosis, and inducing cell proliferation (Gao et al., 2010). Another miRNA important in regulating NF-κB signal transduction pathways is *miR-9*, which directly targets *NF-κB1*, thereby suppressing NF-κB transcriptional activity (**Figure 4**). *miR-9* is downregulated in gastric cancer and *in vitro* studies have shown that restoration of *miR-9* expression suppresses proliferation of gastric cancer cells (Luo et al., 2009; Wan et al., 2010). Cumulatively, these studies demonstrate that aberrant activation of NF-κB signaling as a result of *H. pylori*-induced miRNA dysregulation results in inhibition of apoptosis and increased proliferation, thereby sensitizing cells for subsequent mutagenesis.

miR-451, another downregulated miRNA in *H. pylori*-infected gastric mucosa and gastric cancer, targets *MIF* (macrophage migration inhibitory factor; Bandres et al., 2009), a lymphokine involved in cell-mediated immunity that is expressed in response to *H. pylori* infection and during gastric carcinogenesis (He et al., 2006). Overexpression of *miR-451* results in targeted downregulation of *MIF*, which is accompanied by a decrease in cell proliferation and increased apoptosis (**Figure 4**). Furthermore, there is an inverse correlation between *miR-451* and MIF expression in gastric cancer, suggesting that *miR-451* functions as a tumor suppressor by silencing *MIF* expression, leading to a proliferative and anti-apoptotic phenotype (Bandres et al., 2009). *miR-141*, another miRNA significantly decreased in *H. pylori*-infected gastric tissue (Matsushima et al., 2011) as well as gastric carcinoma, targets *FGFR2* (fibroblast growth factor receptor), and overexpression of *miR-141* leads to decreased FGFR2 expression and inhibition of proliferation (Du et al., 2009; **Figure 4**). *miR-23a* functions as a growth-promoting and anti-apoptotic factor. It is significantly upregulated in gastric adenocarcinoma and targets *IL-6R* (interleukin-6 receptor), which promotes increased proliferation and decreased apoptosis in gastric adenocarcinoma cells (Zhu et al., 2010a; **Figure 4**).

HELICOBACTER PYLORI AND miRNA DYSREGULATION PROMOTES CELL INVASION AND METASTASIS

Invasion and metastasis are hallmarks of cancer cells. Several intracellular signaling pathways, such as those mediated by TGFβ and hepatocyte growth factor/Met signaling, promote metastasis. In addition to its role in regulating cell cycle progression, the *H. pylori* downregulated *miR-449* also targets *Met*, a known proto-oncogene that encodes the hepatocyte growth factor receptor. Aberrant activation of Met triggers oncogenic processes, such as proliferation, angiogenesis, invasion, and metastasis (Bou Kheir et al., 2011; Lize et al., 2011). Thus, the targeted downregulation of *miR-449* by *H. pylori* and during gastric carcinogenesis results in upregulation of Met, increased cell proliferation, and likely other oncogenic processes.

The metastatic potential of cancer cells is also regulated by mechanisms that control cell survival, cytoskeletal changes, as well as the activity of extracellular matrix-degrading proteinases (MMPs). Many miRNAs known to regulate cell cycle progression, proliferation, and apoptosis pathways are also involved in metastasis. For example, overexpression of *miR-21* has been shown to increase the invasiveness of gastric cancer cells. In addition to its known tumor suppressor targets, *miR-21* also targets *RECK* (reversion-inducing-cysteine-rich protein with kazal motifs), a tumor and metastasis suppressor that inhibits tumor metastasis and angiogenesis through modulation of matrix metalloproteinases (MMPs; Zhang et al., 2008). *H. pylori* induces expression of MMPs, including MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, which have been linked to *H. pylori*-induced disease and carcinogenesis (Elkington et al., 2005). These data suggest that *H. pylori* has the potential to modulate expression of MMPs through

dysregulation of host miRNAs and these disruptions may increase the propensity for gastric transformation.

miR-106a is significantly upregulated in cancer cells (Volinia et al., 2006) and is known to correlate with increased lymphatic and distant metastasis (Xiao et al., 2009a). Conversely, *miR-218*, a tumor suppressor miRNA, is downregulated in gastric cancer (Volinia et al., 2006), which correlates with increased metastasis and invasion. This is thought to occur through direct targeting of *ROBO1* (roundabout homolog), which leads to enhanced signaling through the ROBO1 receptor. The SLIT/ROBO signaling pathway has been implicated in many biological responses through regulation of cell migration (Tie et al., 2010). Thus, disruption of this signaling cascade can result in increased invasion and metastasis.

CONCLUSION

The discovery of miRNAs just over a decade ago has challenged the central dogma of genetic and epigenetic regulation. Although extensive work has been dedicated to identifying miRNAs, mRNA targets, and their contribution to accepted regulatory networks, we have only begun to scratch the surface. With thousands of miRNAs within the human genome, and the ability of each miRNA to target and regulate numerous protein-coding mRNAs, affected regulatory networks are likely to be modified by countless miRNA contributors and will continue to evolve.

Many questions arise when comparing miRNA expression profiles in different model systems *in vitro* and *in vivo* and when comparing miRNA expression profiles in *H. pylori*-infected gastric tissue and gastric cancer. For example, *miR-106b*, a known oncogenic miRNA, upregulated in various malignancies including gastric cancer, is decreased in *H. pylori*-infected gastric mucosa. Similarly, *miR-34b*, *miR-34c*, *miR-103*, *miR-200a*, *miR-200b*, *miR-214*, and *miR-372* are all overexpressed in gastric cancer, while in *H. pylori*-infected gastric mucosa these miRNAs are significantly downregulated. In contrast, *miR-146a* is significantly decreased in gastric cancer, but upregulated in *H. pylori*-infected gastric tissue. However, a recent report has shown that *miR-146a* is upregulated in a subset of gastric cancers. Although examining miRNA expression signatures in gastric cancer is clearly important in understanding the disease, development of novel therapeutics requires greater insight into the miRNA profiles in precancerous gastric tissues. Since the majority of gastric cancers arise within the context of chronic inflammation, it will be particularly important to discriminate between preneoplastic and tumor-specific miRNA expression profiles. A more comprehensive understanding of the roles of miRNAs in normal biological processes and disease is needed to fully appreciate miRNA dysregulation by pathogens, such as *H. pylori*. Furthermore, the relationship between single miRNAs and their targets are important to consider, but many of these relationships are cell and context specific. Thus, it is critically important to dissect these intricate pathways and understand how host–pathogen interactions disrupt these encompassing regulatory pathways.

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REFERENCES

Ahn, S. M., Cha, J. Y., Kim, J., Kim, D., Trang, H. T., Kim, Y. M., Cho, Y. H., Park, D., and Hong, S. (2011). Smad3 regulates E-cadherin via miRNA-200 pathway. *Oncogene.* doi: 10.1038/onc.2011.484. [Epub ahead of print].

Akopyants, N. S., Clifton, S. W., Kersulyte, D., Crabtree, J. E., Youree, B. E., Reece, C. A., Bukanov, N. O., Drazek, E. S., Roe, B. A., and Berg, D. E. (1998). Analyses of the cag pathogenicity island of *Helicobacter pylori*. *Mol. Microbiol.* 28, 37–53.

Alm, R. A., Ling, L. S., Moir, D. T., King, B. L., Brown, E. D., Doig, P. C., Smith, D. R., Noonan, B., Guild, B. C., deJonge, B. L., Carmel, G., Tummino, P. J., Caruso, A., Uria-Nickelsen, M., Mills, D. M., Ives, C., Gibson, R., Merberg, D., Mills, S. D., Jiang, Q., Taylor, D. E., Vovis, G. F., and Trust, T. J. (1999). Genomic-sequence comparison of two unrelated isolates of the human gastric pathogen *Helicobacter pylori*. *Nature* 397, 176–180.

Ambros, V. (2004). The functions of animal microRNAs. *Nature* 431, 350–355.

Bandres, E., Bitarte, N., Arias, F., Agorreta, J., Fortes, P., Agirre, X., Zarate, R., Diaz-Gonzalez, J. A., Ramirez, N., Sola, J. J., Jimenez, P., Rodriguez, J., and Garcia-Foncillas, J. (2009). microRNA-451 regulates macrophage migration inhibitory factor production and proliferation of gastrointestinal cancer cells. *Clin. Cancer Res.* 15, 2281–2290.

Bartel, D. P. (2009). microRNAs: target recognition and regulatory functions. *Cell* 136, 215–233.

Belair, C., Baud, J., Chabas, S., Sharma, C. M., Vogel, J., Staedel, C., and Darfeuille, F. (2011). *Helicobacter pylori* interferes with an embryonic stem cell micro RNA cluster to block cell cycle progression. *Silence* 2, 7–23.

Boncristiano, M., Paccani, S. R., Barone, S., Ulivieri, C., Patrussi, L., Ilver, D., Amedei, A., D'Elios, M. M., Telford, J. L., and Baldari, C. T. (2003). The *Helicobacter pylori* vacuolating toxin inhibits T cell activation by two independent mechanisms. *J. Exp. Med.* 198, 1887–1897.

Bou Kheir, T., Futoma-Kazmierczak, E., Jacobsen, A., Krogh, A., Bardram, L., Hother, C., Gronbaek, K., Federspiel, B., Lund, A. H., and Friis-Hansen, L. (2011). miR-449 inhibits cell proliferation and is down-regulated in gastric cancer. *Mol. Cancer* 10, 29–40.

Censini, S., Lange, C., Xiang, Z., Crabtree, J. E., Ghiara, P., Borodovsky, M., Rappuoli, R., and Covacci, A. (1996). cag, a pathogenicity island of Helicobacter pylori, encodes type I- specific and disease-associated virulence factors. *Proc. Natl. Acad. Sci. U.S.A.* 93, 14648–14653.

Chan, S. H., Wu, C. W., Li, A. F., Chi, C. W., and Lin, W. C. (2008). miR-21 microRNA expression in human gastric carcinomas and its clinical association. *Anticancer Res.* 28, 907–911.

Chen, C. Z., Li, L., Lodish, H. F., and Bartel, D. P. (2004). microRNAs modulate hematopoietic lineage differentiation. *Science* 303, 83–86.

Costinean, S., Zanesi, N., Pekarsky, Y., Tili, E., Volinia, S., Heerema, N., and Croce, C. M. (2006). Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in E(mu)-miR155 transgenic mice. *Proc. Natl. Acad. Sci. U.S.A.* 103, 7024–7029.

Covacci, A., Censini, S., Bugnoli, M., Petracca, R., Burroni, D., Macchia, G., Massone, A., Papini, E., Xiang, Z., Figura, N., and Rappuoli, R. (1993). Molecular characterization of the 128-kDa immunodominant antigen of *Helicobacter pylori* associated with cytotoxicity and duodenal ulcer. *Proc. Natl. Acad. Sci. U.S.A.* 90, 5791–5795.

Cover, T. L., and Blaser, M. J. (1992). Purification and characterization of the vacuolating toxin from *Helicobacter pylori*. *J. Biol. Chem.* 267, 10570–10575.

Cover, T. L., Tummuru, M. K., Cao, P., Thompson, S. A., and Blaser, M. J. (1994). Divergence of genetic sequences for the vacuolating cytotoxin among *Helicobacter pylori* strains. *J. Biol. Chem.* 269, 10566–10573.

Craig, V. J., Cogliatti, S. B., Imig, J., Renner, C., Neuenschwander, S., Rehrauer, H., Schlapbach, R., Dirnhofer, S., Tzankov, A., and Muller, A. (2011a). Myc-mediated repression of microRNA-34a promotes high-grade transformation of B-cell lymphoma by dysregulation of FoxP1. *Blood* 117, 6227–6236.

Craig, V. J., Cogliatti, S. B., Rehrauer, H., Wundisch, T., and Muller, A. (2011b). Epigenetic silencing of microRNA-203 dysregulates ABL1 expression and drives *Helicobacter*-associated gastric lymphomagenesis. *Cancer Res.* 71, 3616–3624.

Cui, Y., Su, W. Y., Xing, J., Wang, Y. C., Wang, P., Chen, X. Y., Shen, Z. Y., Cao, H., Lu, Y. Y., and Fang, J. Y. (2011). miR-29a inhibits cell proliferation and induces cell cycle arrest through the downregulation of p42.3 in human gastric cancer. *PLoS ONE* 6, e25872. doi:10.1371/journal.pone.0025872

Ding, L., Xu, Y., Zhang, W., Deng, Y., Si, M., Du, Y., Yao, H., Liu, X., Ke, Y., Si, J., and Zhou, T. (2010). miR-375 frequently downregulated in gastric cancer inhibits cell proliferation by targeting JAK2. *Cell Res.* 20, 784–793.

Du, Y., Xu, Y., Ding, L., Yao, H., Yu, H., Zhou, T., and Si, J. (2009). Down-regulation of miR-141 in gastric cancer and its involvement in cell growth. *J. Gastroenterol.* 44, 556–561.

Elkington, P. T., O'Kane, C. M., and Friedland, J. S. (2005). The paradox of matrix metalloproteinases in infectious disease. *Clin. Exp. Immunol.* 142, 12–20.

El-Omar, E. M., Carrington, M., Chow, W. H., McColl, K. E., Bream, J. H., Young, H. A., Herrera, J., Lissowska, J., Yuan, C. C., Rothman, N., Lanyon, G., Martin, M., Fraumeni, J. F. Jr., and Rabkin, C. S. (2000). Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 404, 398–402.

El-Omar, E. M., Rabkin, C. S., Gammon, M. D., Vaughan, T. L., Risch, H. A., Schoenberg, J. B., Stanford, J. L., Mayne, S. T., Goedert, J., Blot, W. J., Fraumeni, J. F. Jr., and Chow, W. H. (2003). Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology* 124, 1193–1201.

Fassi Fehri, L., Koch, M., Belogolova, E., Khalil, H., Bolz, C., Kalali, B., Mollenkopf, H. J., Beigier-Bompadre, M., Karlas, A., Schneider, T., Churin, Y., Gerhard, M., and Meyer, T. F. (2010). *Helicobacter pylori* induces miR-155 in T cells in a cAMP-Foxp3-dependent manner. *PLoS ONE* 5, e9500. doi:10.1371/journal.pone.0009500

Ferlay, J., Autier, P., Boniol, M., Heanue, M., Colombet, M., and Boyle, P. (2007). Estimates of the cancer incidence and mortality in Europe in 2006. *Ann. Oncol.* 18, 581–592.

Figueiredo, C., Machado, J. C., Pharoah, P., Seruca, R., Sousa, S., Carvalho, R., Capelinha, A. F., Quint, W., Caldas, C., van Doorn, L. J., Carneiro, F., and Sobrinho-Simoes, M. (2002). *Helicobacter pylori* and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. *J. Natl. Cancer Inst.* 94, 1680–1687.

Fu, S., Ramanujam, K. S., Wong, A., Fantry, G. T., Drachenberg, C. B., James, S. P., Meltzer, S. J., and Wilson, K. T. (1999). Increased expression and cellular localization of inducible nitric oxide synthase and cyclooxygenase 2 in *Helicobacter pylori* gastritis. *Gastroenterology* 116, 1319–1329.

Furuta, T., El-Omar, E. M., Xiao, F., Shirai, N., Takashima, M., and Sugimurra, H. (2002). Interleukin 1beta polymorphisms increase risk of hypochlorhydria and atrophic gastritis and reduce risk of duodenal ulcer recurrence in Japan. *Gastroenterology* 123, 92–105.

Gao, C., Zhang, Z., Liu, W., Xiao, S., Gu, W., and Lu, H. (2010). Reduced microRNA-218 expression is associated with high nuclear factor kappa B activation in gastric cancer. *Cancer* 116, 41–49.

Gebert, B., Fischer, W., Weiss, E., Hoffmann, R., and Haas, R. (2003). *Helicobacter pylori* vacuolating cytotoxin inhibits T lymphocyte activation. *Science* 301, 1099–1102.

Gerhard, M., Lehn, N., Neumayer, N., Boren, T., Rad, R., Schepp, W., Miehlke, S., Classen, M., and Prinz, C. (1999). Clinical relevance of the *Helicobacter pylori* gene for blood-group antigen-binding adhesin. *Proc. Natl. Acad. Sci. U.S.A.* 96, 12778–12783.

Goodwin, C. S., Armstrong, J. A., and Marshall, B. J. (1986). *Campylobacter pyloridis*, gastritis, and peptic ulceration. *J. Clin. Pathol.* 39, 353–365.

Guo, J., Miao, Y., Xiao, B., Huan, R., Jiang, Z., Meng, D., and Wang, Y. (2009). Differential expression of microRNA species in human gastric cancer versus non-tumorous tissues. *J. Gastroenterol. Hepatol.* 24, 652–657.

Guo, X., Guo, L., Ji, J., Zhang, J., Chen, X., Cai, Q., Li, J., Gu, Q., Liu, B., Zhu, Z., and Yu, Y. (2010). miRNA-331-3p directly targets E2F1 and induces growth arrest in human gastric cancer. *Biochem. Biophys. Res. Commun.* 398, 1–6.

He, X. X., Yang, J., Ding, Y. W., Liu, W., Shen, Q. Y., and Xia, H. H. (2006). Increased epithelial and serum expression of macrophage migration inhibitory factor (MIF) in gastric cancer: potential role of MIF in gastric carcinogenesis. *Gut* 55, 797–802.

Hessey, S. J., Spencer, J., Wyatt, J. I., Sobala, G., Rathbone, B. J., Axon, A. T., and Dixon, M. F. (1990). Bacterial adhesion and disease activity in *Helicobacter* associated chronic gastritis. *Gut* 31, 134–138.

Ilver, D., Arnqvist, A., Ogren, J., Frick, I. M., Kersulyte, D., Incecik, E. T., Berg, D. E., Covacci, A., Engstrand, L., and Boren, T. (1998). *Helicobacter pylori* adhesin binding fucosylated histo-blood group antigens revealed by retagging. *Science* 279, 373–377.

Ji, Q., Hao, X., Meng, Y., Zhang, M., Desano, J., Fan, D., and Xu, L. (2008). Restoration of tumor suppressor miR-34 inhibits human p53-mutant gastric cancer tumorspheres. *BMC Cancer* 8, 266–277. doi:10.1186/1471-2407-8-266

Juttner, S., Cramer, T., Wessler, S., Walduck, A., Gao, F., Schmitz, F., Wunder, C., Weber, M., Fischer, S. M., Schmidt, W. E., Wiedenmann, B., Meyer, T. F., Naumann, M., and Hocker, M. (2003). *Helicobacter pylori* stimulates host cyclooxygenase-2 gene transcription: critical importance of MEK/ERK-dependent activation of USF1/-2 and CREB transcription factors. *Cell. Microbiol.* 5, 821–834.

Kan, T., Sato, F., Ito, T., Matsumura, N., David, S., Cheng, Y., Agarwal, R., Paun, B. C., Jin, Z., Olaru, A. V., Selaru, F. M., Hamilton, J. P., Yang, J., Abraham, J. M., Mori, Y., and Meltzer, S. J. (2009). The miR-106b-25 polycistron, activated by genomic amplification, functions as an oncogene by suppressing p21 and Bim. *Gastroenterology* 136, 1689–1700.

Kang, Y. H., Lee, H. S., and Kim, W. H. (2002). Promoter methylation and silencing of PTEN in gastric carcinoma. *Lab. Invest.* 82, 285–291.

Kim, Y. K., Yu, J., Han, T. S., Park, S. Y., Namkoong, B., Kim, D. H., Hur, K., Yoo, M. W., Lee, H. J., Yang, H. K., and Kim, V. N. (2009). Functional links between clustered microRNAs: suppression of cell-cycle inhibitors by microRNA clusters in gastric cancer. *Nucleic Acids Res.* 37, 1672–1681.

Kuck, D., Kolmerer, B., Iking-Konert, C., Krammer, P. H., Stremmel, W., and Rudi, J. (2001). Vacuolating cytotoxin of *Helicobacter pylori* induces apoptosis in the human gastric epithelial cell line AGS. *Infect. Immun.* 69, 5080–5087.

Lai, K. W., Koh, K. X., Loh, M., Tada, K., Subramaniam, M. M., Lim, X. Y., Vaithilingam, A., Salto-Tellez, M., Iacopetta, B., Ito, Y., and Soong, R. (2010). microRNA-130b regulates the tumour suppressor RUNX3 in gastric cancer. *Eur. J. Cancer* 46, 1456–1463.

Lam, E. K., Wang, X., Shin, V. Y., Zhang, S., Morrison, H., Sun, J., Ng, E. K., Yu, J., and Jin, H. (2011). A microRNA contribution to aberrant Ras activation in gastric cancer. *Am. J. Transl. Res.* 3, 209–218.

Lee, R. C., Feinbaum, R. L., and Ambros, V. (1993). The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 75, 843–854.

Leunk, R. D., Johnson, P. T., David, B. C., Kraft, W. G., and Morgan, D. R. (1988). Cytotoxic activity in broth-culture filtrates of *Campylobacter pylori*. *J. Med. Microbiol.* 26, 93–99.

Lewis, B. P., Shih, I. H., Jones-Rhoades, M. W., Bartel, D. P., and Burge, C. B. (2003). Prediction of mammalian microRNA targets. *Cell* 115, 787–798.

Li, N., Xu, X., Xiao, B., Zhu, E. D., Li, B. S., Liu, Z., Tang, B., Zou, Q. M., Liang, H. P., and Mao, X. H. (2011a). *H. pylori* related proinflammatory cytokines contribute to the induction of miR-146a in human gastric epithelial cells. *Mol. Biol. Rep.* doi: 10.1007/s11033-011-1257-5. [Epub ahead of print].

Li, X., Zhang, Y., Zhang, H., Liu, X., Gong, T., Li, M., Sun, L., Ji, G., Shi, Y., Han, Z., Han, S., Nie, Y., Chen, X., Zhao, Q., Ding, J., Wu, K., and Daiming, F. (2011b). miRNA-223 promotes gastric cancer invasion and metastasis by targeting tumor suppressor EPB41L3. *Mol. Cancer Res.* 9, 824–833.

Li, Q. L., Ito, K., Sakakura, C., Fukamachi, H., Inoue, K., Chi, X. Z., Lee, K. Y., Nomura, S., Lee, C. W., Han, S. B., Kim, H. M., Kim, W. J., Yamamoto, H., Yamashita, N., Yano, T., Ikeda, T., Itohara, S., Inazawa, J., Abe, T., Hagiwara, A., Yamagishi, H., Ooe, A., Kaneda, A., Sugimura, T., Ushijima, T., Bae, S. C., and Ito, Y. (2002). Causal relationship between the loss of RUNX3 expression and gastric cancer. *Cell* 109, 113–124.

Liu, Z., Xiao, B., Tang, B., Li, B., Li, N., Zhu, E., Guo, G., Gu, J.,

Zhuang, Y., Liu, X., Ding, H., Zhao, X., Guo, H., Mao, X., and Zou, Q. (2010). Up-regulated microRNA-146a negatively modulate *Helicobacter pylori*-induced inflammatory response in human gastric epithelial cells. *Microbes Infect.* 12, 854–863.

Lize, M., Klimke, A., and Dobbelstein, M. (2011). microRNA-449 in cell fate determination. *Cell Cycle* 10, 2874–2882.

Lu, J., Getz, G., Miska, E. A., Alvarez-Saavedra, E., Lamb, J., Peck, D., Sweet-Cordero, A., Ebert, B. L., Mak, R. H., Ferrando, A. A., Downing, J. R., Jacks, T., Horvitz, H. R., and Golub, T. R. (2005). microRNA expression profiles classify human cancers. *Nature* 435, 834–838.

Lu, Z., Liu, M., Stribinskis, V., Klinge, C. M., Ramos, K. S., Colburn, N. H., and Li, Y. (2008). microRNA-21 promotes cell transformation by targeting the programmed cell death 4 gene. *Oncogene* 27, 4373–4379.

Luo, H., Zhang, H., Zhang, Z., Zhang, X., Ning, B., Guo, J., Nie, N., Liu, B., and Wu, X. (2009). Down-regulated miR-9 and miR-433 in human gastric carcinoma. *J. Exp. Clin. Cancer Res.* 28, 82–91.

Machado, J. C., Pharoah, P., Sousa, S., Carvalho, R., Oliveira, C., Figueiredo, C., Amorim, A., Seruca, R., Caldas, C., Carneiro, F., and Sobrinho-Simoes, M. (2001). Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. *Gastroenterology* 121, 823–829.

Mahdavi, J., Sonden, B., Hurtig, M., Olfat, F. O., Forsberg, L., Roche, N., Angstrom, J., Larsson, T., Teneberg, S., Karlsson, K. A., Altraja, S., Wadstrom, T., Kersulyte, D., Berg, D. E., Dubois, A., Petersson, C., Magnusson, K. E., Norberg, T., Lindh, F., Lundskog, B. B., Arnqvist, A., Hammarstrom, L., and Boren, T. (2002). *Helicobacter pylori* SabA adhesin in persistent infection and chronic inflammation. *Science* 297, 573–578.

Marshall, B. J., Armstrong, J. A., McGechie, D. B., and Glancy, R. J. (1985). Attempt to fulfill Koch's postulates for pyloric *Campylobacter*. *Med. J. Aust.* 142, 436–439.

Matsushima, K., Isomoto, H., Inoue, N., Nakayama, T., Hayashi, T., Nakayama, M., Nakao, K., Hirayama, T., and Kohno, S. (2011). microRNA signatures in *Helicobacter pylori*-infected gastric mucosa. *Int. J. Cancer* 128, 361–370.

McCarthy, C. J., Crofford, L. J., Greenson, J., and Scheiman, J. M. (1999). Cyclooxygenase-2 expression in gastric antral mucosa before and after eradication of *Helicobacter pylori* infection. *Am. J. Gastroenterol.* 94, 1218–1223.

Meyer, F., Ramanujam, K. S., Gobert, A. P., James, S. P., and Wilson, K. T. (2003). Cutting edge: cyclooxygenase-2 activation suppresses Th1 polarization in response to *Helicobacter pylori*. *J. Immunol.* 171, 3913–3917.

Motoyama, K., Inoue, H., Mimori, K., Tanaka, F., Kojima, K., Uetake, H., Sugihara, K., and Mori, M. (2010). Clinicopathological and prognostic significance of PDCD4 and microRNA-21 in human gastric cancer. *Int. J. Oncol.* 36, 1089–1095.

Motoyama, K., Inoue, H., Nakamura, Y., Uetake, H., Sugihara, K., and Mori, M. (2008). Clinical significance of high mobility group A2 in human gastric cancer and its relationship to let-7 microRNA family. *Clin. Cancer Res.* 14, 2334–2340.

Nishida, N., Mimori, K., Fabbri, M., Yokobori, T., Sudo, T., Tanaka, F., Shibata, K., Ishii, H., Doki, Y., and Mori, M. (2011). microRNA-125a-5p is an independent prognostic factor in gastric cancer and inhibits the proliferation of human gastric cancer cells in combination with trastuzumab. *Clin. Cancer Res.* 17, 2725–2733.

Oertli, M., Engler, D. B., Kohler, E., Koch, M., Meyer, T. F., and Muller, A. (2011). microRNA-155 is essential for the T cell-mediated control of *Helicobacter pylori* infection and for the induction of chronic gastritis and colitis. *J. Immunol.* 187, 3578–3586.

Okubo, M., Tahara, T., Shibata, T., Yamashita, H., Nakamura, M., Yoshioka, D., Yonemura, J., Ishizuka, T., Arisawa, T., and Hirata, I. (2010). Association between common genetic variants in pre-microRNAs and gastric cancer risk in Japanese population. *Helicobacter* 15, 524–531.

Parkin, D. M. (2006). The global health burden of infection-associated cancers in the year 2002. *Int. J. Cancer* 118, 3030–3044.

Parkin, D. M., Bray, F., Ferlay, J., and Pisani, P. (2005). Global cancer statistics, 2002. *CA Cancer J. Clin.* 55, 74–108.

Petrocca, F., Visone, R., Onelli, M. R., Shah, M. H., Nicoloso, M. S., de Martino, I., Iliopoulos, D., Pilozzi, E., Liu, C. G., Negrini, M., Cavazzini, L., Volinia, S., Alder, H., Ruco, L. P., Baldassarre, G., Croce, C. M., and Vecchione, A. (2008). E2F1-regulated microRNAs impair TGFbeta-dependent cell-cycle arrest and apoptosis in gastric cancer. *Cancer Cell* 13, 272–286.

Phadnis, S. H., Ilver, D., Janzon, L., Normark, S., and Westblom, T. U. (1994). Pathological significance and molecular characterization of the vacuolating toxin gene of *Helicobacter pylori*. *Infect. Immun.* 62, 1557–1565.

Polk, D. B., and Peek, R. M. Jr. (2010). *Helicobacter pylori*: gastric cancer and beyond. *Nat. Rev. Cancer* 10, 403–414.

Ristimaki, A., Honkanen, N., Jankala, H., Sipponen, P., and Harkonen, M. (1997). Expression of cyclooxygenase-2 in human gastric carcinoma. *Cancer Res.* 57, 1276–1280.

Romano, M., Ricci, V., Memoli, A., Tuccillo, C., Di Popolo, A., Sommi, P., Acquaviva, A. M., Del Vecchio Blanco, C., Bruni, C. B., and Zarrilli, R. (1998). *Helicobacter pylori* upregulates cyclooxygenase-2 mRNA expression and prostaglandin E2 synthesis in MKN28 gastric mucosal cells in vitro. *J. Biol. Chem.* 273, 28560–28563.

Saito, Y., Murata-Kamiya, N., Hirayama, T., Ohba, Y., and Hatakeyama, M. (2010). Conversion of *Helicobacter pylori* CagA from senescence inducer to oncogenic driver through polarity-dependent regulation of p21. *J. Exp. Med.* 207, 2157–2174.

Saito, Y., Suzuki, H., Tsugawa, H., Nakagawa, I., Matsuzaki, J., Kanai, Y., and Hibi, T. (2009). Chromatin remodeling at Alu repeats by epigenetic treatment activates silenced microRNA-512-5p with downregulation of Mcl-1 in human gastric cancer cells. *Oncogene* 28, 2738–2744.

Saito, Y., Suzuki, H., Tsugawa, H., Suzuki, S., Matsuzaki, J., Hirata, K., and Hibi, T. (2011). Dysfunctional gastric emptying with down-regulation of muscle-specific microRNAs in *Helicobacter pylori*-infected mice. *Gastroenterology* 140, 189–198.

Sasaki, N., Morisaki, T., Hashizume, K., Yao, T., Tsuneyoshi, M., Noshiro, H., Nakamura, K., Yamanaka, T., Uchiyama, A., Tanaka, M., and Katano, M. (2001). Nuclear factor-kappaB p65 (RelA) transcription factor is constitutively activated in human gastric carcinoma tissue. *Clin. Cancer Res.* 7, 4136–4142.

Sawaoka, H., Kawano, S., Tsuji, S., Tsuji, M., Sun, W., Gunawan, E. S., and Hori, M. (1998). *Helicobacter pylori* infection induces cyclooxygenase-2 expression in human gastric mucosa. *Prostaglandins Leukot. Essent. Fatty Acids* 59, 313–316.

Schmitt, W., and Haas, R. (1994). Genetic analysis of the *Helicobacter pylori* vacuolating cytotoxin: structural similarities with the IgA protease type of exported protein. *Mol. Microbiol.* 12, 307–319.

Shinozaki, A., Sakatani, T., Ushiku, T., Hino, R., Isogai, M., Ishikawa, S., Uozaki, H., Takada, K., and Fukayama, M. (2010). Downregulation of microRNA-200 in EBV-associated gastric carcinoma. *Cancer Res.* 70, 4719–4727.

Shirin, H., Weinstein, I. B., and Moss, S. F. (2001). Effects of *H. pylori* infection of gastric epithelial cells on cell cycle control. *Front. Biosci.* 6, E104–E118.

Sonkoly, E., and Pivarcsi, A. (2009). Advances in microRNAs: implications for immunity and inflammatory diseases. *J. Cell. Mol. Med.* 13, 24–38.

Sun, T., Wang, C., Xing, J., and Wu, D. (2011). miR-429 modulates the expression of c-myc in human gastric carcinoma cells. *Eur. J. Cancer*. doi: 10.1016/j.ejca.2011.05.021. [Epub ahead of print].

Sundrud, M. S., Torres, V. J., Unutmaz, D., and Cover, T. L. (2004). Inhibition of primary human T cell proliferation by *Helicobacter pylori* vacuolating toxin (VacA) is independent of VacA effects on IL-2 secretion. *Proc. Natl. Acad. Sci. U.S.A.* 101, 7727–7732.

Sung, J. J., Leung, W. K., Go, M. Y., To, K. F., Cheng, A. S., Ng, E. K., and Chan, F. K. (2000). Cyclooxygenase-2 expression in *Helicobacter pylori*-associated premalignant and malignant gastric lesions. *Am. J. Pathol.* 157, 729–735.

Suzuki, H., Yamamoto, E., Nojima, M., Kai, M., Yamano, H. O., Yoshikawa, K., Kimura, T., Kudo, T., Harada, E., Sugai, T., Takamaru, H., Niinuma, T., Maruyama, R., Yamamoto, H., Tokino, T., Imai, K., Toyota, M., and Shinomura, Y. (2010). Methylation-associated silencing of microRNA-34b/c in gastric cancer and its involvement in an epigenetic field defect. *Carcinogenesis* 31, 2066–2073.

Tang, B., Xiao, B., Liu, Z., Li, N., Zhu, E. D., Li, B. S., Xie, Q. H., Zhuang, Y., Zou, Q. M., and Mao, X. H. (2010). Identification of MyD88 as a novel target of miR-155, involved in negative regulation of *Helicobacter pylori*-induced inflammation. *FEBS Lett.* 584, 1481–1486.

Telford, J. L., Ghiara, P., Dell'Orco, M., Comanducci, M., Burroni, D., Bugnoli, M., Tecce, M. F., Censini, S., Covacci, A., Xiang, Z., Papini, E.,

Montecucco, C., Parente, L., and Rappuoli, R. (1994). Gene structure of the *Helicobacter pylori* cytotoxin and evidence of its key role in gastric disease. *J. Exp. Med.* 179, 1653–1658.

Thai, T. H., Calado, D. P., Casola, S., Ansel, K. M., Xiao, C., Xue, Y., Murphy, A., Frendewey, D., Valenzuela, D., Kutok, J. L., Schmidt-Supprian, M., Rajewsky, N., Yancopoulos, G., Rao, A., and Rajewsky, K. (2007). Regulation of the germinal center response by microRNA-155. *Science* 316, 604–608.

Tie, J., Pan, Y., Zhao, L., Wu, K., Liu, J., Sun, S., Guo, X., Wang, B., Gang, Y., Zhang, Y., Li, Q., Qiao, T., Zhao, Q., Nie, Y., and Fan, D. (2010). miR-218 inhibits invasion and metastasis of gastric cancer by targeting the Robo1 receptor. *PLoS Genet.* 6, e1000879. doi:10.1371/journal.pgen.1000879

Tomb, J. F., White, O., Kerlavage, A. R., Clayton, R. A., Sutton, G. G., Fleischmann, R. D., Ketchum, K. A., Klenk, H. P., Gill, S., Dougherty, B. A., Nelson, K., Quackenbush, J., Zhou, L., Kirkness, E. F., Peterson, S., Loftus, B., Richardson, D., Dodson, R., Khalak, H. G., Glodek, A., McKenney, K., Fitzegerald, L. M., Lee, N., Adams, M. D., Hickey, E. K., Berg, D. E., Gocayne, J. D., Utterback, T. R., Peterson, J. D., Kelley, J. M., Cotton, M. D., Weidman, J. M., Fujii, C., Bowman, C., Watthey, L., Wallin, E., Hayes, W. S., Borodovsky, M., Karp, P. D., Smith, H. O., Fraser, C. M., and Venter, J. C. (1997). The complete genome sequence of the gastric pathogen *Helicobacter pylori*. *Nature* 388, 539–547.

Tsukamoto, Y., Nakada, C., Noguchi, T., Tanigawa, M., Nguyen, L. T., Uchida, T., Hijiya, N., Matsuura, K., Fujioka, T., Seto, M., and Moriyama, M. (2010). microRNA-375 is downregulated in gastric carcinomas and regulates cell survival by targeting PDK1 and 14-3-3zeta. *Cancer Res.* 70, 2339–2349.

Tummuru, M. K., Cover, T. L., and Blaser, M. J. (1993). Cloning and expression of a high-molecular-mass major antigen of *Helicobacter pylori*: evidence of linkage to cytotoxin production. *Infect. Immun.* 61, 1799–1809.

Unoki, M., and Nakamura, Y. (2003). EGR2 induces apoptosis in various cancer cell lines by direct transactivation of BNIP3L and BAK. *Oncogene* 22, 2172–2185.

Varambally, S., Cao, Q., Mani, R. S., Shankar, S., Wang, X., Ateeq, B., Laxman, B., Cao, X., Jing, X., Ramnarayanan, K., Brenner, J. C., Yu, J., Kim, J. H., Han, B., Tan, P., Kumar-Sinha, C., Lonigro, R. J., Palanisamy, N., Maher, C. A., and Chinnaiyan, A. M. (2008). Genomic loss of microRNA-101 leads to overexpression of histone methyltransferase EZH2 in cancer. *Science* 322, 1695–1699.

Viala, J., Chaput, C., Boneca, I. G., Cardona, A., Girardin, S. E., Moran, A. P., Athman, R., Memet, S., Huerre, M. R., Coyle, A. J., DiStefano, P. S., Sansonetti, P. J., Labigne, A., Bertin, J., Philpott, D. J., and Ferrero, R. L. (2004). Nod1 responds to peptidoglycan delivered by the *Helicobacter pylori* cag pathogenicity island. *Nat. Immunol.* 5, 1166–1174.

Volinia, S., Calin, G. A., Liu, C. G., Ambs, S., Cimmino, A., Petrocca, F., Visone, R., Iorio, M., Roldo, C., Ferracin, M., Prueitt, R. L., Yanaihara, N., Lanza, G., Scarpa, A., Vecchione, A., Negrini, M., Harris, C. C., and Croce, C. M. (2006). A microRNA expression signature of human solid tumors defines cancer gene targets. *Proc. Natl. Acad. Sci. U.S.A.* 103, 2257–2261.

Wan, H. Y., Guo, L. M., Liu, T., Liu, M., Li, X., and Tang, H. (2010). Regulation of the transcription factor NF-kappaB1 by microRNA-9 in human gastric adenocarcinoma. *Mol. Cancer* 9, 16.

Wang, H. J., Ruan, H. J., He, X. J., Ma, Y. Y., Jiang, X. T., Xia, Y. J., Ye, Z. Y., and Tao, H. Q. (2010). microRNA-101 is down-regulated in gastric cancer and involved in cell migration and invasion. *Eur. J. Cancer* 46, 2295–2303.

Wu, C. Y., Wang, C. J., Tseng, C. C., Chen, H. P., Wu, M. S., Lin, J. T., Inoue, H., and Chen, G. H. (2005). *Helicobacter pylori* promote gastric cancer cells invasion through a NF-kappaB and COX-2-mediated pathway. *World J. Gastroenterol.* 11, 3197–3203.

Wu, F., Zikusoka, M., Trindade, A., Dassopoulos, T., Harris, M. L., Bayless, T. M., Brant, S. R., Chakravarti, S., and Kwon, J. H. (2008). microRNAs are differentially expressed in ulcerative colitis and alter expression of macrophage inflammatory peptide-2 alpha. *Gastroenterology* 135, 1624–1635.e24.

Wu, Q., Jin, H., Yang, Z., Luo, G., Lu, Y., Li, K., Ren, G., Su, T., Pan, Y., Feng, B., Xue, Z., Wang, X., and Fan, D. (2010). miR-150 promotes gastric cancer proliferation by negatively regulating the pro-apoptotic gene EGR2. *Biochem. Biophys. Res. Commun.* 392, 340–345.

Xia, H. H., and Talley, N. J. (2001). Apoptosis in gastric epithelium induced by *Helicobacter pylori* infection: implications in gastric carcinogenesis. *Am. J. Gastroenterol.* 96, 16–26.

Xia, L., Zhang, D., Du, R., Pan, Y., Zhao, L., Sun, S., Hong, L., Liu, J., and Fan, D. (2008). miR-15b and miR-16 modulate multidrug resistance by targeting BCL2 in human gastric cancer cells. *Int. J. Cancer* 123, 372–379.

Xiao, B., Guo, J., Miao, Y., Jiang, Z., Huan, R., Zhang, Y., Li, D., and Zhong, J. (2009a). Detection of miR-106a in gastric carcinoma and its clinical significance. *Clin. Chim. Acta* 400, 97–102.

Xiao, B., Liu, Z., Li, B. S., Tang, B., Li, W., Guo, G., Shi, Y., Wang, F., Wu, Y., Tong, W. D., Guo, H., Mao, X. H., and Zou, Q. M. (2009b). Induction of microRNA-155 during *Helicobacter pylori* infection and its negative regulatory role in the inflammatory response. *J. Infect. Dis.* 200, 916–925.

Xiao, B., Zhu, E. D., Li, N., Lu, D. S., Li, W., Li, B. S., Zhao, Y. L., Mao, X. H., Guo, G., Yu, P. W., and Zou, Q. M. (2011). Increased miR-146a in gastric cancer directly targets SMAD4 and is involved in modulating cell proliferation and apoptosis. *Oncol. Rep.* doi: 10.3892/or.2011.1514. [Epub ahead of print].

Xu, X., Li, W., Fan, X., Liang, Y., Zhao, M., Zhang, J., Tong, W., Wang, J., Yang, W., and Lu, Y. (2007). Identification and characterization of a novel p42.3 gene as tumor-specific and mitosis phase-dependent expression in gastric cancer. *Oncogene* 26, 7371–7379.

Yamanaka, Y., Tagawa, H., Takahashi, N., Watanabe, A., Guo, Y. M., Iwamoto, K., Yamashita, J., Saitoh, H., Kameoka, Y., Shimizu, N., Ichinohasama, R., and Sawada, K. (2009). Aberrant overexpression of microRNAs activate AKT signaling via down-regulation of tumor suppressors in natural killer-cell lymphoma/leukemia. *Blood* 114, 3265–3275.

Yang, Q., Jie, Z., Cao, H., Greenlee, A. R., Yang, C., Zou, F., and Jiang, Y. (2011). Low-level expression of let-7a in gastric cancer and its involvement in tumorigenesis by targeting RAB40C. *Carcinogenesis* 32, 713–722.

Yao, Y., Suo, A. L., Li, Z. F., Liu, L. Y., Tian, T., Ni, L., Zhang, W. G., Nan, K. J., Song, T. S., and Huang, C. (2009). microRNA profiling of human gastric cancer. *Mol. Med. Report* 2, 963–970.

Yoo, Y. D., Choi, J. Y., Lee, S. J., Kim, J. S., Min, B. R., Lee, Y. I., and Kang, Y. K. (1999). TGF-beta-induced cell-cycle arrest through the p21(WAF1/CIP1)-G1 cyclin/Cdks-p130 pathway in gastric-carcinoma cells. *Int. J. Cancer* 83, 512–517.

Zhang, Z., Li, Z., Gao, C., Chen, P., Chen, J., Liu, W., Xiao, S., and Lu, H. (2008). miR-21 plays a pivotal role in gastric cancer pathogenesis and progression. *Lab. Invest.* 88, 1358–1366.

Zhu, L. H., Liu, T., Tang, H., Tian, R. Q., Su, C., Liu, M., and Li, X. (2010a). microRNA-23a promotes the growth of gastric adenocarcinoma cell line MGC803 and downregulates interleukin-6 receptor. *FEBS J.* 277, 3726–3734.

Zhu, W., Shan, X., Wang, T., Shu, Y., and Liu, P. (2010b). miR-181b modulates multidrug resistance by targeting BCL2 in human cancer cell lines. *Int. J. Cancer* 127, 2520–2529.

Zhu, W., Xu, H., Zhu, D., Zhi, H., Wang, T., Wang, J., Jiang, B., Shu, Y., and Liu, P. (2011a). miR-200bc/429 cluster modulates multidrug resistance of human cancer cell lines by targeting BCL2 and XIAP. *Cancer Chemother. Pharmacol.* doi: 10.1007/s00280-011-1752-3. [Epub ahead of print].

Zhu, W., Zhu, D., Lu, S., Wang, T., Wang, J., Jiang, B., Shu, Y., and Liu, P. (2011b). miR-497 modulates multidrug resistance of human cancer cell lines by targeting BCL2. *Med. Oncol.* doi: 10.1007/s12032-010-9797-4. [Epub ahead of print].

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APPENDIX

Table A1 | miRNAs downregulated in gastric cancer.

miRNAs	Target mRNAs*	Biological processes targeted	Reference
let-7a	*RAB40C*	Cell cycle progression	Li et al. (2010, 2011c), Motoyama et al. (2008), Tsujiura et al. (2010), Yang et al. (2011), Zhang et al. (2007), Zhu et al. (2010c)
		Proliferation	
	HMGA2	**Invasion**	
miR-9	*CDX2*	Cell cycle progression	Luo et al. (2009), Rotkrua et al. (2011), Tsai et al. (2011a), Wan et al. (2010)
	NFκB1		
	GRB2, RAB34	Proliferation	
miR-15b	*BCL2*	Apoptosis	Xia et al. (2008)
miR-16	*BCL2*	Apoptosis	Shin et al. (2011), Xia et al. (2008)
miR-29a	*p42.3*	Cell cycle progression	Cui et al. (2011), Lang et al. (2010)
		Proliferation	
	CDC42	Invasion	
miR-29b	*CDC42*	Proliferation	Lang et al. (2010)
		Invasion	
miR-29c	*CDC42*	Proliferation	Lang et al. (2010)
		Invasion	
miR-30a	ND	ND	Li et al. (2010)
miR-30b	ND	ND	Ueda et al. (2010)
miR-30c	ND	ND	Ueda et al. (2010)
miR-31	**ND**	**ND**	Guo et al. (2009), Zhang et al. (2010b)
miR-33b	ND	ND	Volinia et al. (2006)
miR-34	*BCL2*	Apoptosis	Ji et al. (2008)
miR-96	ND	ND	Volinia et al. (2006)
miR-101	***COX-2, FOS***	**Proliferation**	Varambally et al. (2008), Wang et al. (2010)
	MCL1	**Apoptosis**	
	EZH2	**Invasion migration**	
miR-126	*CRK*	Cell cycle progression	Feng et al. (2010), Li et al. (2010, 2011c), Otsubo et al. (2011)
		Proliferation	
		Invasion and metastasis	
	SOX2	Proliferation	
miR-128b	ND	ND	Katada et al. (2009)
miR-129	*CDK6*	Cell cycle progression	Katada et al. (2009), Shen et al. (2010), Tsai et al. (2011b), Wu et al. (2010a)
		Proliferation	
	SOX4	Apoptosis	
miR-133b	ND	ND	Guo et al. (2009), Wu et al. (2011a)
miR-136	ND	ND	Ueda et al. (2010)
miR-138	ND	ND	Volinia et al. (2006)
miR-139-5p	ND	ND	Guo et al. (2009)
miR-141	***FGFR2***	**Proliferation**	Du et al. (2009)
miR-143	ND	Proliferation	Li et al. (2011a), Takagi et al. (2009), Wu et al. (2011a)
miR-145	ND	ND	Li et al. (2011a), Takagi et al. (2009), Tchernitsa et al. (2010)
miR-146a	*IRAK1, TRAF6*	Immune response	Hou et al. (2011), Kogo et al. (2011), Li et al. (2011a,d), Okubo et al. (2010), Tchernitsa et al. (2010)
		Proliferation	
		Apoptosis	
miR-148	ND	ND	Katada et al. (2009)
miR-148a	*CCKBR*	Proliferation	Chen et al. (2010), Guo et al. (2011), Zheng et al. (2011)
	p27	Cell cycle progression	
	ROCK1	Invasion and metastasis	
miR-148b	*CCKBR*	Proliferation	Song et al. (2011)
miR-152	*CCKBR*	Proliferation	Chen et al. (2010), Ueda et al. (2010)

(Continued)

Table A1 | Continued

miRNAs	Target mRNAs*	Biological processes targeted	Reference
miR-181b	*BCL2*	Apoptosis	Jiang et al. (2011), Li et al. (2011c), Zhu et al. (2010b)
miR-181c	*NOTCH4, KRAS*	Proliferation	Hashimoto et al. (2010), Zhu et al. (2010b)
	BCL2	Apoptosis	
miR-195	ND	ND	Guo et al. (2009), Wu et al. (2011a)
miR-197	ND	ND	Li et al. (2011c)
miR-203	***ABL1***	**Proliferation**	Chiang et al. (2011), Craig et al. (2011b)
		Invasion	
miR-210	**ND**	**ND**	Li et al. (2011c)
miR-212	*MECP2*	Proliferation	Volinia et al. (2006), Wada et al. (2010), Wu et al. (2011a), Xu et al. (2010)
	MYC		
miR-218	***ECOP***	**Proliferation**	Gao et al. (2010), Tie et al. (2010), Ueda et al. (2010), Volinia et al. (2006)
		Apoptosis	
	ROBO1	**Invasion and metastasis**	
miR-331-3p	*E2F1*	Cell cycle progression	Guo et al. (2010)
		Proliferation	
miR-339	*ICAM-1*	Immune response	Ueda et al. (2009)
miR-375	***PDK1, 14-3-3***	**Apoptosis**	Ding et al. (2010), Tsukamoto et al. (2010), Ueda et al. (2010), Xu et al. (2011)
	JAK2	**Proliferation**	
miR-378	ND	ND	Guo et al. (2009), Yao et al. (2009)
miR-433	*GRB2*	Proliferation	Luo et al. (2009)
miR-449	***GMNN,CCNE2***	**Cell cycle progression**	Bou Kheir et al. (2011), Lize et al. (2011)
	MET, SIRT1	**Proliferation**	
miR-451	*MIF*	Proliferation	Bandres et al. (2009)
		Apoptosis	
miR-497	*BCL2*	Apoptosis	Guo et al. (2009), Zhu et al. (2011b)
miR-512-5p	*MCL1*	Apoptosis	Saito et al. (2009)
miR-638	ND	ND	Yao et al. (2009)
miR-768-3p	ND	ND	Guo et al. (2009)

**Target criteria included (1) reduced protein expression upon miRNA transfection in gastric cells or expression inversely correlated with miRNA in gastric tissue or (2) presence of miRNA binding site on the 3′ UTR of target mRNA confirmed by luciferase reporter assay. ND, target mRNA or biological process not determined. Bold indicates miRNA also downregulated following H. pylori infection.*

Table A2 | miRNAs upregulated in gastric cancer.

miRNAs	Target mRNAs*	Biological processes targeted	Reference
miR-7	ND	ND	Volinia et al. (2006), Wu et al. (2011b)
miR-17	**ND**	**ND**	Guo et al. (2009), Volinia et al. (2006), Yao et al. (2009), Zhou et al. (2010)
miR-17-5p	ND	ND	Petrocca et al. (2008), Tsujiura et al. (2010), Ueda et al. (2010), Volinia et al. (2006)
miR-18a	ND	ND	Guo et al. (2009), Yao et al. (2009)
miR-18b	ND	ND	Guo et al. (2009)
miR-19a	ND	ND	Guo et al. (2009), Ueda et al. (2010)
miR-20a	**ND**	**ND**	Guo et al. (2009), Volinia et al. (2006)
miR-20b	ND	ND	Guo et al. (2009), Katada et al. (2009), Ueda et al. (2010)
miR-21	***PDCD4***	**Proliferation**	Chan et al. (2008), Guo et al. (2009), Li et al. (2010, 2011c), Lu et al. (2008), Motoyama et al. (2010), Petrocca et al. (2008), Shin et al. (2011),
	RECK	**Apoptosis**	Tsujiura et al. (2010), Ueda et al. (2010), Volinia et al. (2006), Zhang et al. (2008)
	PTEN	**Invasion**	
miR-23a	*IL-6R*	Proliferation Apoptosis	Li et al. (2011c), Volinia et al. (2006), Zhu et al. (2010a)
miR-23b	ND	ND	Li et al. (2011c)
miR-24	*AE1*	Proliferation Differentiation	Chan et al. (2010), Volinia et al. (2006), Wu et al. (2010b)
miR-25	*p57*	Cell cycle progression	Kan et al. (2009), Kim et al. (2009), Li et al. (2011c), Petrocca et al. (2008), Ueda et al. (2010), Volinia et al. (2006)
	BIM	Apoptosis	
miR-27	*APC*	Epithelial to mesenchymal transition (EMT)	Zhang et al. (2011)
miR-27a	*PHB*	Proliferation	Katada et al. (2009), Li et al. (2011a); Liu et al. (2009), Sun et al. (2010), Zhao et al. (2011)
	ZBTB10	Metastasis	
miR-34a	*SIRT1*	Cell cycle progression	Craig et al. (2011a), Yamakuchi and Lowenstein (2009), Yao et al. (2009)
	FOXP1	Proliferation	
miR-34b	ND	ND	Katada et al. (2009), Suzuki et al. (2010), Tsai et al. (2011b)
miR-34c	ND	ND	Katada et al. (2009), Suzuki et al. (2010)
miR-92	ND	ND	Li et al. (2011c), Petrocca et al. (2008), Ueda et al. (2010), Volinia et al. (2006)
miR-93	*p21*	Cell cycle progression	Kim et al. (2009), Petrocca et al. (2008), Ueda et al. (2010)
	BIM	Apoptosis	
miR-98	ND	ND	Yao et al. (2009)
miR-99a	ND	ND	Li et al. (2011c)
miR-99b	ND	ND	Volinia et al. (2006)
miR-103	ND	ND	Li et al. (2011c), Tchernitsa et al. (2010), Volinia et al. (2006)
miR-106a	*RB1*	Cell cycle progression Proliferation	Guo et al. (2009), Petrocca et al. (2008), Tsujiura et al. (2010), Ueda et al. (2010), Volinia et al. (2006), Xiao et al. (2009a), Yao et al. (2009)
miR-106b	*p21*	Cell cycle progression	Guo et al. (2009), Kim et al. (2009), Petrocca et al. (2008), Tsujiura et al. (2010), Ueda et al. (2010), Yao et al. (2009)
	BIM	Apoptosis	
miR-107	*CDK6*	Proliferation	Feng et al. (2011), Li et al. (2011b,c), Volinia et al. (2006)
	DICER	Invasion and metastasis	
miR-125b	ND	ND	Li et al. (2011c), Ueda et al. (2010), Volinia et al. (2006)
miR-128a	ND	ND	Katada et al. (2009)
miR-130b	*RUNX3*	Apoptosis	Li et al. (2002), Lai et al. (2010), Yao et al. (2009)
miR-135a	ND	ND	Ueda et al. (2010)
miR-138	ND	ND	Yao et al. (2009)
miR-146a	***SMAD4***	**Proliferation** **Apoptosis**	Xiao et al. (2011)
miR-147	ND	ND	Yao et al. (2009)
miR-150	*EGR2*	Apoptosis	Katada et al. (2009), Wu et al. (2010c)

(Continued)

Table A2 | Continued

miRNAs	Target mRNAs*	Biological processes targeted	Reference
miR-155	***IKK-ε, SMAD2***	**Immune response**	Fassi Fehri et al. (2010), Oertli et al. (2011), Tang et al. (2010), Thai et al. (2007), Volinia et al. (2006), Xiao et al. (2009b), Yao et al. (2011)
	FADD, PKIα	**Apoptosis**	
miR-181a-2	ND	ND	Yao et al. (2009)
miR-185	ND	ND	Yao et al. (2009)
miR-191	*NDST1*	Proliferation	Li et al. (2011c), Shi et al. (2011), Ueda et al. (2010), Volinia et al. (2006)
miR-192	*ALCAM*	Proliferation	Jin et al. (2011), Volinia et al. (2006)
miR-196a	ND	ND	Okubo et al. (2010), Yao et al. (2009)
miR-200a	*ZEB1, ZEB2*	Epithelial to mesenchymal transition (EMT)	Ahn et al. (2011)
miR-200b	*ZEB1, ZEB2*	EMT	Ahn et al. (2011), Zhu et al. (2011a)
	BCL2, XIAP	Apoptosis	
miR-214	ND	ND	Li et al. (2011c), Ueda et al. (2010), Volinia et al. (2006)
miR-215	*ALCAM*	Proliferation	Jin et al. (2011), Volinia et al. (2006)
		Apoptosis	
miR-221	*p27, p57*	Cell cycle progression	Chun-Zhi et al. (2010), Kim et al. (2009), Li et al. (2011c), Volinia et al. (2006), Yao et al. (2009)
	PTEN	Proliferation	
miR-222	*p27, p57*	Cell cycle progression	Chun-Zhi et al. (2010), Kim et al. (2009), Li et al. (2011c), Ueda et al. (2009), Volinia et al. (2006)
	PTEN	Proliferation	
	ICAM-1	Immune response	
miR-223	***EPB41L3***	**Invasion and metastasis**	Li et al. (2011c), Petrocca et al. (2008), Volinia et al. (2006), Yao et al. (2009)
miR-302f	ND	ND	Yao et al. (2009)
miR-337-3p	ND	ND	Yao et al. (2009)
miR-340	ND	ND	Guo et al. (2009), Yao et al. (2009)
miR-345	ND	ND	Ueda et al. (2010)
miR-372	*LATS2*	Cell cycle progression	Cho et al. (2009)
		Apoptosis	
miR-421	*CBX7, RBMXL1*	Proliferation	Guo et al. (2009), Jiang et al. (2010)
miR-520c-3p	ND	ND	Yao et al. (2009)
miR-575	ND	ND	Yao et al. (2009)
miR-601	ND	ND	Yao et al. (2009)
miR-616	ND	ND	Yao et al. (2009)
miR-650	*ING4*	Apoptosis	Zhang et al. (2010a)
miR-658	ND	ND	Guo et al. (2009)
miR-1259	ND	ND	Yao et al. (2009)

**Target criteria included (1) reduced protein expression upon miRNA transfection in gastric cells or expression inversely correlated with miRNA in gastric tissue or (2) presence of miRNA binding site on the 3′ UTR of target mRNA confirmed by luciferase reporter assay. ND, target mRNA or biological process not determined. Bold indicates miRNA also upregulated following H. pylori infection.*

REFERENCES

Ahn, S. M., Cha, J. Y., Kim, J., Kim, D., Trang, H. T., Kim, Y. M., Cho, Y. H., Park, D., and Hong, S. (2011). Smad3 regulates E-cadherin via miRNA-200 pathway. *Oncogene.* doi: 10.1038/onc.2011.484. [Epub ahead of print].

Bandres, E., Bitarte, N., Arias, F., Agorreta, J., Fortes, P., Agirre, X., Zarate, R., Diaz-Gonzalez, J. A., Ramirez, N., Sola, J. J., Jimenez, P., Rodriguez, J., and Garcia-Foncillas, J. (2009). microRNA-451 regulates macrophage migration inhibitory factor production and proliferation of gastrointestinal cancer cells. *Clin. Cancer Res.* 15, 2281–2290.

Bou Kheir, T., Futoma-Kazmierczak, E., Jacobsen, A., Krogh, A., Bardram, L., Hother, C., Gronbaek, K., Federspiel, B., Lund, A. H., and Friis-Hansen, L. (2011). miR-449 inhibits cell proliferation and is down-regulated in gastric cancer. *Mol. Cancer* 10, 29–41.

Chan, M. C., Hilyard, A. C., Wu, C., Davis, B. N., Hill, N. S., Lal, A., Lieberman, J., Lagna, G., and Hata, A. (2010). Molecular basis for antagonism between PDGF and the TGF-beta family of signalling pathways by control of miR-24 expression. *EMBO J.* 29, 559–573.

Chan, S. H., Wu, C. W., Li, A. F., Chi, C. W., and Lin, W. C. (2008). miR-21 microRNA expression in human gastric carcinomas and its clinical association. *Anticancer Res.* 28, 907–911.

Chen, Y., Song, Y., Wang, Z., Yue, Z., Xu, H., Xing, C., and Liu, Z. (2010). Altered expression of miR-148a and miR-152 in gastrointestinal cancers and its clinical significance. *J. Gastrointest. Surg.* 14, 1170–1179.

Chiang, Y., Song, Y., Wang, Z., Chen, Y., Yue, Z., Xu, H., Xing, C., and Liu, Z. (2011). Aberrant expression of miR-203 and its clinical significance in gastric and colorectal cancers. *J. Gastrointest. Surg.* 15, 63–70.

Cho, W. J., Shin, J. M., Kim, J. S., Lee, M. R., Hong, K. S., Lee, J. H., Koo, K. H., Park, J. W., and Kim, K. S. (2009). miR-372 regulates cell cycle and apoptosis of AGS human gastric cancer cell line through direct regulation of LATS2. *Mol. Cells* 28, 521–527.

Chun-Zhi, Z., Lei, H., An-Ling, Z., Yan-Chao, F., Xiao, Y., Guang-Xiu, W., Zhi-Fan, J., Pei-Yu, P., Qing-Yu, Z., and Chun-Sheng, K. (2010). microRNA-221 and microRNA-222 regulate gastric carcinoma cell proliferation and radioresistance by targeting PTEN. *BMC Cancer* 10, 367–377. doi:10.1186/1471-2407-10-367

Craig, V. J., Cogliatti, S. B., Imig, J., Renner, C., Neuenschwander, S., Rehrauer, H., Schlapbach, R., Dirnhofer, S., Tzankov, A., and Muller, A. (2011a). Myc-mediated repression of microRNA-34a promotes high-grade transformation of B-cell lymphoma by dysregulation of FoxP1. *Blood* 117, 6227–6236.

Craig, V. J., Cogliatti, S. B., Rehrauer, H., Wundisch, T., and Muller, A. (2011b). Epigenetic silencing of microRNA-203 dysregulates ABL1 expression and drives *Helicobacter*-associated gastric lymphomagenesis. *Cancer Res.* 71, 3616–3624.

Cui, Y., Su, W. Y., Xing, J., Wang, Y. C., Wang, P., Chen, X. Y., Shen, Z. Y., Cao, H., Lu, Y. Y., and Fang, J. Y. (2011). miR-29a inhibits cell proliferation and induces cell cycle arrest through the downregulation of p42.3 in human gastric cancer. *PLoS ONE* 6, e25872. doi:10.1371/journal.pone.0025872

Ding, L., Xu, Y., Zhang, W., Deng, Y., Si, M., Du, Y., Yao, H., Liu, X., Ke, Y., Si, J., and Zhou, T. (2010). miR-375 frequently downregulated in gastric cancer inhibits cell proliferation by targeting JAK2. *Cell Res.* 20, 784–793.

Du, Y., Xu, Y., Ding, L., Yao, H., Yu, H., Zhou, T., and Si, J. (2009). Down-regulation of miR-141 in gastric cancer and its involvement in cell growth. *J. Gastroenterol.* 44, 556–561.

Fassi Fehri, L., Koch, M., Belogolova, E., Khalil, H., Bolz, C., Kalali, B., Mollenkopf, H. J., Beigier-Bompadre, M., Karlas, A., Schneider, T., Churin, Y., Gerhard, M., and Meyer, T. F. (2010). *Helicobacter pylori* induces miR-155 in T cells in a cAMP-Foxp3-dependent manner. *PLoS ONE* 5, e9500. doi:10.1371/journal.pone.0009500

Feng, L., Xie, Y., Zhang, H., and Wu, Y. (2011). miR-107 targets cyclin-dependent kinase 6 expression, induces cell cycle G1 arrest and inhibits invasion in gastric cancer cells. *Med. Oncol.* doi: 10.1007/s12032-011-9823-1. [Epub ahead of print].

Feng, R., Chen, X., Yu, Y., Su, L., Yu, B., Li, J., Cai, Q., Yan, M., Liu, B., and Zhu, Z. (2010). miR-126 functions as a tumour suppressor in human gastric cancer. *Cancer Lett.* 298, 50–63.

Gao, C., Zhang, Z., Liu, W., Xiao, S., Gu, W., and Lu, H. (2010). Reduced microRNA-218 expression is associated with high nuclear factor kappa B activation in gastric cancer. *Cancer* 116, 41–49.

Guo, J., Miao, Y., Xiao, B., Huan, R., Jiang, Z., Meng, D., and Wang, Y. (2009). Differential expression of microRNA species in human gastric cancer versus non-tumorous tissues. *J. Gastroenterol. Hepatol.* 24, 652–657.

Guo, S. L., Peng, Z., Yang, X., Fan, K. J., Ye, H., Li, Z. H., Wang, Y., Xu, X. L., Li, J., Wang, Y. L., and Teng, Y. (2011). miR-148a promoted cell proliferation by targeting p27 in gastric cancer cells. *Int. J. Biol. Sci.* 7, 567–574.

Guo, X., Guo, L., Ji, J., Zhang, J., Chen, X., Cai, Q., Li, J., Gu, Q., Liu, B., Zhu, Z., and Yu, Y. (2010). miRNA-331-3p directly targets E2F1 and induces growth arrest in human gastric cancer. *Biochem. Biophys. Res. Commun.* 398, 1–6.

Hashimoto, Y., Akiyama, Y., Otsubo, T., Shimada, S., and Yuasa, Y. (2010). Involvement of epigenetically silenced microRNA-181c in gastric carcinogenesis. *Carcinogenesis* 31, 777–784.

Hou, Z., Xie, L., Yu, L., Qian, X., and Liu, B. (2011). microRNA-146a is down-regulated in gastric cancer and regulates cell proliferation and apoptosis. *Med. Oncol.* doi: 10.1007/s12032-011-9862-7. [Epub ahead of print].

Ji, Q., Hao, X., Meng, Y., Zhang, M., Desano, J., Fan, D., and Xu, L. (2008). Restoration of tumor suppressor miR-34 inhibits human p53-mutant gastric cancer tumorspheres. *BMC Cancer* 8, 266–278. doi:10.1186/1471-2407-8-266

Jiang, J., Zheng, X., Xu, X., Zhou, Q., Yan, H., Zhang, X., Lu, B., Wu, C., and Ju, J. (2011). Prognostic significance of miR-181b and miR-21 in gastric cancer patients treated with S-1/oxaliplatin or doxifluridine/oxaliplatin. *PLoS ONE* 6, e23271. doi:10.1371/journal.pone.0023271

Jiang, Z., Guo, J., Xiao, B., Miao, Y., Huang, R., Li, D., and Zhang, Y. (2010). Increased expression of miR-421 in human gastric carcinoma and its clinical association. *J. Gastroenterol.* 45, 17–23.

Jin, Z., Selaru, F. M., Cheng, Y., Kan, T., Agarwal, R., Mori, Y., Olaru, A. V., Yang, J., David, S., Hamilton, J. P., Abraham, J. M., Harmon, J., Duncan, M., Montgomery, E. A., and Meltzer, S. J. (2011). microRNA-192 and -215 are upregulated in human gastric cancer in vivo and suppress ALCAM expression in vitro. *Oncogene* 30, 1577–1585.

Kan, T., Sato, F., Ito, T., Matsumura, N., David, S., Cheng, Y., Agarwal, R., Paun, B. C., Jin, Z., Olaru, A. V., Selaru, F. M., Hamilton, J. P., Yang, J., Abraham, J. M., Mori, Y., and Meltzer, S. J. (2009). The miR-106b-25 polycistron, activated by genomic amplification, functions as an oncogene by suppressing p21 and Bim. *Gastroenterology* 136, 1689–1700.

Katada, T., Ishiguro, H., Kuwabara, Y., Kimura, M., Mitui, A., Mori, Y., Ogawa, R., Harata, K., and Fujii, Y. (2009). microRNA expression profile in undifferentiated gastric cancer. *Int. J. Oncol.* 34, 537–542.

Kim, Y. K., Yu, J., Han, T. S., Park, S. Y., Namkoong, B., Kim, D. H., Hur, K., Yoo, M. W., Lee, H. J., Yang, H. K., and Kim, V. N. (2009). Functional links between clustered microRNAs: suppression of cell-cycle inhibitors by microRNA clusters in gastric cancer. *Nucleic Acids Res.* 37, 1672–1681.

Kogo, R., Mimori, K., Tanaka, F., Komune, S., and Mori, M. (2011). Clinical significance of miR-146a in gastric cancer cases. *Clin. Cancer Res.* 17, 4277–4284.

Lai, K. W., Koh, K. X., Loh, M., Tada, K., Subramaniam, M. M., Lim, X., Vaithilingam, A., Salto-Tellez, M., Iacopetta, B., Ito, Y., and Soong, R. (2010). microRNA-130b regulates the tumour suppressor RUNX3 in gastric cancer. *Eur. J. Cancer* 46, 1456–1463.

Lang, N., Liu, M., Tang, Q. L., Chen, X., Liu, Z., and Bi, F. (2010). Effects of microRNA-29 family members on proliferation and invasion of gastric cancer cell lines. *Chin. J. Cancer* 29, 603–610.

Li, Q. L., Ito, K., Sakakura, C., Fukamachi, H., Inoue, K., Chi, X. Z., Lee, K. Y., Nomura, S., Lee, C. W., Han, S. B., Kim, H. M., Kim, W. J., Yamamoto, H., Yamashita, N., Yano, T., Ikeda, T., Itohara, S., Inazawa, J., Abe, T., Hagiwara, A., Yamagishi, H., Ooe, A., Kaneda, A., Sugimura, T., Ushijima, T., Bae, S. C., and Ito, Y. (2002). Causal relationship between the loss of RUNX3 expression and gastric cancer. *Cell* 109, 113–124.

Li, X., Luo, F., Li, Q., Xu, M., Feng, D., Zhang, G., and Wu, W. (2011a). Identification of new aberrantly expressed miRNAs in intestinal-type. *Oncol. Rep.* 26, 1431–1439.

Li, X., Zhang, Y., Shi, Y., Dong, G., Liang, J., Han, Y., Wang, X., Zhao, Q., Ding, J., Wu, K., and Fan, D. (2011b). microRNA-107, an oncogene microRNA that regulates tumour invasion and metastasis by targeting DICER1 in gastric cancer. *J. Cell. Mol. Med.* 15, 1887–1895.

Li, X., Zhang, Y., Zhang, H., Liu, X., Gong, T., Li, M., Sun, L., Ji, G., Shi, Y., Han, Z., Han, S., Nie, Y., Chen, X., Zhao, Q., Ding, J., Wu, K., and Daiming, F. (2011c). miRNA-223 promotes gastric cancer invasion and metastasis by targeting tumor suppressor EPB41L3. *Mol. Cancer Res.* 9, 824–833.

Li, N., Xu, X., Xiao, B., Zhu, E. D., Li, B. S., Liu, Z., Tang, B., Zou, Q. M., Liang, H. P., and Mao, X. H. (2011d). *H. pylori* related proinflammatory cytokines contribute to the induction of miR-146a in human gastric epithelial cells. *Mol. Biol. Rep.* doi: 10.1007/s11033-011-1257-5. [Epub ahead of print].

Li, X., Zhang, Y., Ding, J., Wu, K., and Fan, D. (2010). Survival prediction of gastric cancer by a seven-microRNA signature. *Gut* 59, 579–585.

Liu, T., Tang, H., Lang, Y., Liu, M., and Li, X. (2009). microRNA-27a functions as an oncogene in gastric adenocarcinoma by targeting prohibitin. *Cancer Lett.* 273, 233–242.

Lize, M., Klimke, A., and Dobbelstein, M. (2011). microRNA-449 in cell fate determination. *Cell Cycle* 10, 2874–2882.

Lu, Z., Liu, M., Stribinskis, V., Klinge, C. M., Ramos, K. S., Colburn, N. H., and Li, Y. (2008). microRNA-21 promotes cell transformation by targeting the programmed cell death 4 gene. *Oncogene* 27, 4373–4379.

Luo, H., Zhang, H., Zhang, Z., Zhang, X., Ning, B., Guo, J., Nie, N., Liu, B., and Wu, X. (2009). Down-regulated miR-9 and miR-433 in human gastric carcinoma. *J. Exp. Clin. Cancer Res.* 28, 82–91.

Motoyama, K., Inoue, H., Mimori, K., Tanaka, F., Kojima, K., Uetake, H., Sugihara, K., and Mori, M. (2010). Clinicopathological and prognostic significance of PDCD4 and microRNA-21 in human gastric cancer. *Int. J. Oncol.* 36, 1089–1095.

Motoyama, K., Inoue, H., Nakamura, Y., Uetake, H., Sugihara, K., and Mori, M. (2008). Clinical significance of high mobility group A2 in human gastric cancer and its relationship to let-7 microRNA family. *Clin. Cancer Res.* 14, 2334–2340.

Oertli, M., Engler, D. B., Kohler, E., Koch, M., Meyer, T. F., and Muller, A. (2011). MicroRNA-155 is essential for the T cell-mediated control of *Helicobacter pylori* infection and for the induction of chronic gastritis and colitis. *J. Immunol.* 187, 3578–3586.

Okubo, M., Tahara, T., Shibata, T., Yamashita, H., Nakamura, M., Yoshioka, D., Yonemura, J., Ishizuka, T., Arisawa, T., and Hirata, I. (2010). Association between common genetic variants in pre-microRNAs and gastric cancer risk in Japanese population. *Helicobacter* 15, 524–531.

Otsubo, T., Akiyama, Y., Hashimoto, Y., Shimada, S., Goto, K., and Yuasa, Y. (2011). microRNA-126 inhibits SOX2 expression and contributes to gastric carcinogenesis. *PLoS ONE* 6, e16617. doi:10.1371/journal.pone.0016617

Petrocca, F., Visone, R., Onelli, M. R., Shah, M. H., Nicoloso, M. S., de Martino, I., Iliopoulos, D., Pilozzi, E., Liu, C. G., Negrini, M., Cavazzini, L., Volinia, S., Alder, H., Ruco, L. P., Baldassarre, G., Croce, C. M., and Vecchione, A. (2008). E2F1-regulated microRNAs impair TGFbeta-dependent cell-cycle arrest and apoptosis in gastric cancer. *Cancer Cell* 13, 272–286.

Rotkrua, P., Akiyama, Y., Hashimoto, Y., Otsubo, T., and Yuasa, Y. (2011). miR-9 downregulates CDX2 expression in gastric cancer cells. *Int. J. Cancer* 129, 2611–2620.

Saito, Y., Suzuki, H., Tsugawa, H., Nakagawa, I., Matsuzaki, J., Kanai, Y., and Hibi, T. (2009). Chromatin remodeling at Alu repeats by epigenetic treatment activates silenced microRNA-512-5p with downregulation of Mcl-1 in human gastric cancer cells. *Oncogene* 28, 2738–2744.

Shen, R., Pan, S., Qi, S., Lin, X., and Cheng, S. (2010). Epigenetic repression of microRNA-129-2 leads to overexpression of SOX4 in gastric cancer. *Biochem. Biophys. Res. Commun.* 394, 1047–1052.

Shi, X., Su, S., Long, J., Mei, B., and Chen, Y. (2011). microRNA-191 targets N-deacetylase/N-sulfotransferase 1 and promotes cell growth in human gastric carcinoma cell line MGC803. *Acta Biochim. Biophys. Sin.* doi: 10.1093/abbs/gmr084. [Epub ahead of print].

Shin, V. Y., Jin, H., Ng, E. K., Cheng, A. S., Chong, W. W., Wong, C. Y., Leung, W. K., Sung, J. J., and Chu, K. M. (2011). NF-kappaB targets miR-16 and miR-21 in gastric cancer: involvement of prostaglandin E receptors. *Carcinogenesis* 32, 240–245.

Song, Y. X., Yue, Z. Y., Wang, Z. N., Xu, Y. Y., Luo, Y., Xu, H. M., Zhang, X., Jiang, L., Xing, C. Z., and Zhang, Y. (2011). microRNA-148b is frequently down-regulated in gastric cancer and acts as a tumor suppressor by inhibiting cell proliferation. *Mol. Cancer* 10, 1–13.

Sun, Q., Gu, H., Zeng, Y., Xia, Y., Wang, Y., Jing, Y., Yang, L., and Wang, B. (2010). Hsa-mir-27a genetic variant contributes to gastric cancer susceptibility through affecting miR-27a and target gene expression. *Cancer Sci.* 101, 2241–2247.

Suzuki, H., Yamamoto, E., Nojima, M., Kai, M., Yamano, H. O., Yoshikawa, K., Kimura, T., Kudo, T., Harada, E., Sugai, T., Takamaru, H., Niinuma, T., Maruyama, R., Yamamoto, H., Tokino, T., Imai, K., Toyota, M., and Shinomura, Y. (2010). Methylation-associated silencing of microRNA-34b/c in gastric cancer and its involvement in an epigenetic field defect. *Carcinogenesis* 31, 2066–2073.

Takagi, T., Iio, A., Nakagawa, Y., Naoe, T., Tanigawa, N., and Akao, Y. (2009). Decreased expression of microRNA-143 and -145 in human gastric cancers. *Oncology* 77, 12–21.

Tang, B., Xiao, B., Liu, Z., Li, N., Zhu, E. D., Li, B. S., Xie, Q. H., Zhuang, Y., Zou, Q. M., and Mao, X. H. (2010). Identification of MyD88 as a novel target of miR-155, involved in negative regulation of *Helicobacter pylori*-induced inflammation. *FEBS Lett.* 584, 1481–1486.

Tchernitsa, O., Kasajima, A., Schafer, R., Kuban, R. J., Ungethum, U., Gyorffy, B., Neumann, U., Simon, E., Weichert, W., Ebert, M. P., and Rocken, C. (2010). Systematic evaluation of the miRNA-ome and its downstream effects on mRNA expression identifies gastric cancer progression. *J. Pathol.* 222, 310–319.

Thai, T. H., Calado, D. P., Casola, S., Ansel, K. M., Xiao, C., Xue, Y., Murphy, A., Frendewey, D., Valenzuela, D., Kutok, J. L., Schmidt-Supprian, M., Rajewsky, N., Yancopoulos, G., Rao, A., and Rajewsky, K. (2007). Regulation of the germinal center response by microRNA-155. *Science* 316, 604–608.

Tie, J., Pan, Y., Zhao, L., Wu, K., Liu, J., Sun, S., Guo, X., Wang, B., Gang, Y., Zhang, Y., Li, Q., Qiao, T., Zhao, Q., Nie, Y., and Fan, D. (2010). miR-218 inhibits invasion and metastasis of gastric cancer by targeting the Robo1 receptor. *PLoS Genet.* 6, e1000879. doi:10.1371/journal.pgen.1000879

Tsai, K. W., Liao, Y. L., Wu, C. W., Hu, L. Y., Li, S. C., Chan, W. C., Ho, M. R., Lai, C. H., Kao, H. W., Fang, W. L., Huang, K. H., and Lin, W. C. (2011a). Aberrant hypermethylation of miR-9 genes in gastric cancer. *Epigenetics* 6, 1189–1197.

Tsai, K. W., Wu, C. W., Hu, L. Y., Li, S. C., Liao, Y. L., Lai, C. H., Kao, H. W., Fang, W. L., Huang, K. H., Chan, W. C., and Lin, W. C. (2011b). Epigenetic regulation of miR-34b and miR-129 expression in gastric cancer. *Int. J. Cancer* 129, 2600–2610.

Tsujiura, M., Ichikawa, D., Komatsu, S., Shiozaki, A., Takeshita, H., Kosuga, T., Konishi, H., Morimura, R., Deguchi, K., Fujiwara, H., Okamoto, K., and Otsuji, E. (2010). Circulating microRNAs in plasma of patients with gastric cancers. *Br. J. Cancer* 102, 1174–1179.

Tsukamoto, Y., Nakada, C., Noguchi, T., Tanigawa, M., Nguyen, L. T., Uchida, T., Hijiya, N., Matsuura, K., Fujioka, T., Seto, M., and Moriyama, M. (2010). microRNA-375 is downregulated in gastric carcinomas and regulates cell survival by targeting PDK1 and 14-3-3zeta. *Cancer Res.* 70, 2339–2349.

Ueda, R., Kohanbash, G., Sasaki, K., Fujita, M., Zhu, X., Kastenhuber, E. R., McDonald, H. A., Potter, D. M., Hamilton, R. L., Lotze, M. T., Khan, S. A., Sobol, R. W., and Okada, H. (2009). Dicer-regulated microRNAs 222 and 339 promote resistance of cancer cells to cytotoxic T-lymphocytes by down-regulation of ICAM-1. *Proc. Natl. Acad. Sci. U.S.A.* 106, 10746–10751.

Ueda, T., Volinia, S., Okumura, H., Shimizu, M., Taccioli, C., Rossi, S., Alder, H., Liu, C. G., Oue, N., Yasui, W., Yoshida, K., Sasaki, H., Nomura, S., Seto, Y., Kaminishi, M., Calin, G. A., and Croce, C. M. (2010). Relation between microRNA expression and progression and prognosis of gastric cancer: a microRNA expression analysis. *Lancet Oncol.* 11, 136–146.

Varambally, S., Cao, Q., Mani, R. S., Shankar, S., Wang, X., Ateeq, B., Laxman, B., Cao, X., Jing, X., Ramnarayanan, K., Brenner, J. C., Yu, J., Kim, J. H., Han, B., Tan, P., Kumar-Sinha, C., Lonigro, R. J., Palanisamy, N., Maher, C. A., and Chinnaiyan, A. M. (2008). Genomic loss of microRNA-101 leads to overexpression of histone methyltransferase EZH2 in cancer. *Science* 322, 1695–1699.

Volinia, S., Calin, G. A., Liu, C. G., Ambs, S., Cimmino, A., Petrocca, F., Visone, R., Iorio, M., Roldo, C., Ferracin, M., Prueitt, R. L., Yanaihara, N., Lanza, G., Scarpa, A., Vecchione, A., Negrini, M., Harris, C. C., and Croce, C. M. (2006). A microRNA expression signature of human solid tumors defines cancer gene targets. *Proc. Natl. Acad. Sci. U.S.A.* 103, 2257–2261.

Wada, R., Akiyama, Y., Hashimoto, Y., Fukamachi, H., and Yuasa,

Y. (2010). miR-212 is downregulated and suppresses methyl-CpG-binding protein MeCP2 in human gastric cancer. *Int. J. Cancer* 127, 1106–1114.

Wan, H. Y., Guo, L. M., Liu, T., Liu, M., Li, X., and Tang, H. (2010). Regulation of the transcription factor NF-kappaB1 by microRNA-9 in human gastric adenocarcinoma. *Mol. Cancer* 9, 16–26.

Wang, H. J., Ruan, H. J., He, X. J., Ma, Y. Y., Jiang, X. T., Xia, Y. J., Ye, Z. Y., and Tao, H. Q. (2010). microRNA-101 is down-regulated in gastric cancer and involved in cell migration and invasion. *Eur. J. Cancer* 46, 2295–2303.

Wu, J., Qian, J., Li, C., Kwok, L., Cheng, F., Liu, P., Perdomo, C., Kotton, D., Vaziri, C., Anderlind, C., Spira, A., Cardoso, W. V., and Lu, J. (2010a). miR-129 regulates cell proliferation by downregulating Cdk6 expression. *Cell Cycle* 9, 1809–1818.

Wu, J., Zhang, Y. C., Suo, W. H., Liu, X. B., Shen, W. W., Tian, H., and Fu, G. H. (2010b). Induction of anion exchanger-1 translation and its opposite roles in the carcinogenesis of gastric cancer cells and differentiation of K562 cells. *Oncogene* 29, 1987–1996.

Wu, Q., Jin, H., Yang, Z., Luo, G., Lu, Y., Li, K., Ren, G., Su, T., Pan, Y., Feng, B., Xue, Z., Wang, X., and Fan, D. (2010c). miR-150 promotes gastric cancer proliferation by negatively regulating the pro-apoptotic gene EGR2. *Biochem. Biophys. Res. Commun.* 392, 340–345.

Wu, W. Y., Xue, X. Y., Chen, Z. J., Han, S. L., Huang, Y. P., Zhang, L. F., Zhu, G. B., and Shen, X. (2011a). Potentially predictive microRNAs of gastric cancer with metastasis to lymph node. *World J. Gastroenterol.* 17, 3645–3651.

Wu, X. M., Shao, X. Q., Meng, X. X., Zhang, X. N., Zhu, L., Liu, S. X., Lin, J., and Xiao, H. S. (2011b). Genome-wide analysis of microRNA and mRNA expression signatures in hydroxycamptothecin-resistant gastric cancer cells. *Acta Pharmacol. Sin.* 32, 259–269.

Xia, L., Zhang, D., Du, R., Pan, Y., Zhao, L., Sun, S., Hong, L., Liu, J., and Fan, D. (2008). miR-15b and miR-16 modulate multidrug resistance by targeting BCL2 in human gastric cancer cells. *Int. J. Cancer* 123, 372–379.

Xiao, B., Guo, J., Miao, Y., Jiang, Z., Huan, R., Zhang, Y., Li, D., and Zhong, J. (2009a). Detection of miR-106a in gastric carcinoma and its clinical significance. *Clin. Chim. Acta* 400, 97–102.

Xiao, B., Liu, Z., Li, B. S., Tang, B., Li, W., Guo, G., Shi, Y., Wang, F., Wu, Y., Tong, W. D., Guo, H., Mao, X. H., and Zou, Q. M. (2009b). Induction of microRNA-155 during *Helicobacter pylori* infection and its negative regulatory role in the inflammatory response. *J. Infect. Dis.* 200, 916–925.

Xiao, B., Zhu, E. D., Li, N., Lu, D. S., Li, W., Li, B. S., Zhao, Y. L., Mao, X. H., Guo, G., Yu, P. W., and Zou, Q. M. (2011). Increased miR-146a in gastric cancer directly targets SMAD4 and is involved in modulating cell proliferation and apoptosis. *Oncol. Rep.* doi: 10.3892/or.2011.1514. [Epub ahead of print].

Xu, L., Wang, F., Xu, X. F., Mo, W. H., Xia, Y. J., Wan, R., Wang, X. P., and Guo, C. Y. (2010). Down-regulation of miR-212 expression by DNA hypermethylation in human gastric cancer cells. *Med. Oncol.* doi: 10.1007/s12032-010-9691-0. [Epub ahead of print].

Xu, Y., Deng, Y., Yan, X., and Zhou, T. (2011). Targeting miR-375 in gastric cancer. *Expert Opin. Ther. Targets* 15, 961–972.

Yamakuchi, M., and Lowenstein, C. J. (2009). miR-34, SIRT1 and p53: the feedback loop. *Cell Cycle* 8, 712–715.

Yang, Q., Jie, Z., Cao, H., Greenlee, A. R., Yang, C., Zou, F., and Jiang, Y. (2011). Low-level expression of let-7a in gastric cancer and its involvement in tumorigenesis by targeting RAB40C. *Carcinogenesis* 32, 713–722.

Yao, R., Ma, Y., Du, Y., Liao, M., Li, H., Liang, W., Yuan, J., Zhijunma, Yu, X., Xiao, H., and Liao, Y. (2011). The altered expression of inflammation-related microRNAs with microRNA-155 expression correlates with Th17 differentiation in patients with acute coronary syndrome. *Cell. Mol. Immunol.* doi: 10.1038/cmi.2011.22. [Epub ahead of print].

Yao, Y., Suo, A. L., Li, Z. F., Liu, L. Y., Tian, T., Ni, L., Zhang, W. G., Nan, K. J., Song, T. S., and Huang, C. (2009). microRNA profiling of human gastric cancer. *Mol. Med. Report* 2, 963–970.

Zhang, H. H., Wang, X. J., Li, G. X., Yang, E., and Yang, N. M. (2007). Detection of let-7a microRNA by real-time PCR in gastric carcinoma. *World J. Gastroenterol.* 13, 2883–2888.

Zhang, X., Zhu, W., Zhang, J., Huo, S., Zhou, L., Gu, Z., and Zhang, M. (2010a). microRNA-650 targets ING4 to promote gastric cancer tumorigenicity. *Biochem. Biophys. Res. Commun.* 395, 275–280.

Zhang, Y., Guo, J., Li, D., Xiao, B., Miao, Y., Jiang, Z., and Zhuo, H. (2010b). Down-regulation of miR-31 expression in gastric cancer tissues and its clinical significance. *Med. Oncol.* 27, 685–689.

Zhang, Z., Li, Z., Gao, C., Chen, P., Chen, J., Liu, W., Xiao, S., and Lu, H. (2008). miR-21 plays a pivotal role in gastric cancer pathogenesis and progression. *Lab. Invest.* 88, 1358–1366.

Zhang, Z., Liu, S., Shi, R., and Zhao, G. (2011). miR-27 promotes human gastric cancer cell metastasis by inducing epithelial-to-mesenchymal transition. *Cancer Genet.* 204, 486–491.

Zhao, X., Yang, L., and Hu, J. (2011). Down-regulation of miR-27a might inhibit proliferation and drug resistance of gastric cancer cells. *J. Exp. Clin. Cancer Res.* 30, 55–60.

Zheng, B., Liang, L., Wang, C., Huang, S., Cao, X., Zha, R., Liu, L., Jia, D., Tian, Q., Wu, J., Ye, Y. W., Wang, Q., Long, Z., Zhou, Y., Du, C., He, X., and Shi, Y. (2011). microRNA-148a suppresses tumor cell invasion and metastasis by downregulating ROCK1 in gastric cancer. *Clin. Cancer Res.* doi: 10.1158/1078-0432.CCR-11-1714. [Epub ahead of print].

Zhou, H., Guo, J. M., Lou, Y. R., Zhang, X. J., Zhong, F. D., Jiang, Z., Cheng, J., and Xiao, B. X. (2010). Detection of circulating tumor cells in peripheral blood from patients with gastric cancer using microRNA as a marker. *J. Mol. Med.* 88, 709–717.

Zhu, L. H., Liu, T., Tang, H., Tian, R. Q., Su, C., Liu, M., and Li, X. (2010a). microRNA-23a promotes the growth of gastric adenocarcinoma cell line MGC803 and downregulates interleukin-6 receptor. *FEBS J.* 277, 3726–3734.

Zhu, W., Shan, X., Wang, T., Shu, Y., and Liu, P. (2010b). miR-181b modulates multidrug resistance by targeting BCL2 in human cancer cell lines. *Int. J. Cancer* 127, 2520–2529.

Zhu, Y. M., Zhong, Z. X., and Liu, Z. M. (2010c). Relationship between let-7a and gastric mucosa cancerization and its significance. *World J. Gastroenterol.* 16, 3325–3329.

Zhu, W., Xu, H., Zhu, D., Zhi, H., Wang, T., Wang, J., Jiang, B., Shu, Y., and Liu, P. (2011a). miR-200bc/429 cluster modulates multidrug resistance of human cancer cell lines by targeting BCL2 and XIAP. *Cancer Chemother. Pharmacol.* doi: 10.1007/s00280-011-1752-3. [Epub ahead of print].

Zhu, W., Zhu, D., Lu, S., Wang, T., Wang, J., Jiang, B., Shu, Y., and Liu, P. (2011b). miR-497 modulates multidrug resistance of human cancer cell lines by targeting BCL2. *Med. Oncol.* doi: 10.1007/s12032-010-9797-4. [Epub ahead of print].