MicroRNA: a bridge from *H. pylori* infection to gastritis and gastric cancer development

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**INTRODUCTION**

According to the American Cancer Society (ACS), cancer is the second most common death cause in the United States1. Even though the survival rate (up to 5-years) has improved tremendously over the last decades, it is expected that more than 1.5 million Americans will die to cancer in 2012 (Siegel et al., 2012). The incidence and mortality of gastric cancer has followed that of most cancers but still more than 10,000 deaths are expected to happened in 2012 (1.3% of all cancer cases and 7.5% of digestive system cancers; Siegel et al., 2012). According to the Surveillance Epidemiology and End Results (SEER)2, gastric cancer is a disease of disparities, in terms of incidence and mortality, with African American men and women having the highest incidence and mortality rates of gastric cancer when compared to other races/ethnic groups. In addition, males from all ethnicities have higher incidence and mortality rates than females (see text footnote 2). There are several theories to explain these differences and based on several facts, it seems that estrogens are important modulators of gastric cancer risk (Camargo et al., 2012). Additional disparities in gastric cancer incidence and mortality rates are observed by geographic region with Japan and China having more than 20 cases of gastric cancer and North America presenting less than 10 cases per 100,000 individuals (Parkin, 2004; Parkin et al., 2005). All these observations led to the idea that environmental factors, including diet, play a major role in gastric cancer risk. However, recent findings have suggested a significant role of the genetic background in gastric cancer susceptibility. There have been plenty of publications showing association of single nucleotide polymorphisms (SNP) and risk of gastric cancer. We have shown also that these SNPs may serve as biomarkers of risk even at earlier stages, during the progression of inflammatory to malignant gastric stages (Zabaleta et al., 2006, 2008; Zabaleta, 2012). Identifying early markers of risk of GC is crucial because the disease has one of the highest rates of mortality worldwide. However, this task has been complicated by several factors, including difficulties for tissue collection (which is generally obtained by gastric biopsies); the presence of millions of SNPs in the genome and the lack of studies determining the degree of interactions among them; the time-dependent expression of genes which leads to misinterpretation of gene profiles; and very especially, the lack of studies validating genomic profiles generated from tissue samples in more easily obtained samples.

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1 http://www.cancer.org
2 http://seer.cancer.gov/statfacts/html/stomach.html
like blood or urine, making replication of results less invasive and less hazardous and stressful for the patient.

**microRNA**

Since its discovery, microRNA (miRNA) added a new chapter in the study of gene regulation. It was initially observed that the expression of the heterochronic protein, which control temporal development, Lin-14 during the development of *Caenorhabditis elegans* (*C. elegans*) lead to a temporal expression of several cell lineages (Ruvkun and Giusto, 1989). This temporal expression of Lin-14 protein leading to different genotypes suggested a strong regulation in the gene encoding its expression, *Lin-14*. It was later discovered that the expression of Lin-14 protein was downregulated at the post-transcriptional level by two products of the gene *Lin-4*, another heterochronic gene, whose products bind to the untranslated (UTR) 3′ region of the *Lin-14* gene (Wightman et al., 1993). In an interesting series of papers published in the same issue of Science Magazine, three back-to-back papers showed that these small RNA molecules were present in organisms other than *C. elegans*, and the authors coined the term miRNA for them (Lagos-Quintana et al., 2001; Lau et al., 2001; Lee and Ambros, 2001). These miRNA result from the activity of two RNase III, Drosha, and Dicer, that process the primary miRNA into mature miRNA of 18–24 nucleotides that mediate inhibition of translation or degradation of messenger RNA (mRNA; Bartel, 2004) by base mispairing with mRNA (RNAI; Olsen and Ambros, 1999), giving the miRNAs a broad potential to regulate gene expression (Bartel and Chen, 2004). However, the degree of specificity for the binding of the miRNA with its target mRNA seems to be given by the first nine 5′ nucleotides (seed nucleotides) of the miRNA and their complementary 3′ untranslated regions (3′ UTR) in their targets (Moss et al., 1997; Reinhart et al., 2000; Kiriakidou et al., 2004; Vella et al., 2004).

**miRNA NOMENCLATURE**

The criteria for the identification of nucleotide sequences as miRNA were consented by a group of experts on the topic (Ambros et al., 2003). These researchers delineated certain characteristics that, except for some specific conditions, should be met by the sequence to be considered a miRNA, including the detection of a ~22 nt RNA molecule, identification of that molecule on a pool of cDNA made from RNA with specified sizes, the presence of a hairpin, phylogenetic conservation of the molecule and its precursor, and increased expression of the precursor RNA molecules in the absence of Dicer (Ambros et al., 2003). miRNAs are named based on several criteria, including: three or four letters to designate species (e.g., hsa for *Homo sapiens*); mature miRNAs are given the designation of “mir”; sequential numbers; miRNAs that differ in only one or two nucleotides are given letter suffixes, i.e., mmu-miR-10a and mmu-miR-10b; if two different miRNAs are generated from the opposite arms of the hairpin are named with an additional suffix indicating the 5′ or the 3′ where the miRNA is generated from, i.e., hsa-miR-140-5p and hsa-miR-140-3p; in addition, when two miRNAs originate from opposite arms of the hairpin, the one with reduced expression is annotated with an asterisk (*; Ambros et al., 2003; Griffiths-Jones, 2005; Griffiths-Jones et al., 2006, 2008).

**miRNA AND HELICOBACTER PYLORI INFECTION**

Among several factors, infection with *Helicobacter pylori* (*H. pylori*; Ambros et al., 2003) is considered to be a crucial event associated with risk of gastric cancer. Such is the importance of the infection in the inflammation that leads to gastric cancer that *H. pylori* has been classified as a Type I carcinogen by the International Agency for Research in Cancer (IARC; IARC, 1994). After infection to the gastric mucosa, *H. pylori* injects the product of the cytokinin-associated gene (cag; CagA) into the gastric epithelial cells by a type IV secretion system (Backert et al., 2000; Odenbreit et al., 2000). Once there, CagA is phosphorylated (Stein et al., 2002) and induces a cascade of kinases activation leading to cellular changes (Higashi et al., 2002) and production of inflammatory cytokines (Orsini et al., 2000; Lai et al., 2011). Interestingly, using an *in vitro* system, it was shown that CagA induces hsa-miR-584 and hsa-miR-1290 in a NFκB and Erk 1/2 dependent manner, respectively (Zhu et al., 2012). Another set of experiments has shown that after *H. pylori* infection there is a strong induction of hsa-miR-155 which inhibits the production of the potent pro-inflammatory cytokine IL-8, through the inhibition of the NFκB pathway by interacting with the 3′-UTR of the IkB kinase (Xiao et al., 2009; reviewed in Ma et al., 2011). Interestingly, in addition to hsa-miR-155, *H. pylori* infection also induced hsa-miR-146a (Xiao et al., 2009). This miRNA, in addition to hsa-miR-155 and hsa-miR-132, is produced in response to inflammatory stimulus like LPS (Taganov et al., 2006). Interestingly, similar to hsa-miR-155, miR-146 also regulates the NFκB pathway by targeting TRAF6 and IRAK1 (Taganov et al., 2006; Liu et al., 2010). Through the regulation of TRAF6 and IRAK1, hsa-miR-146a modulates the inflammatory response induced by *H. pylori* by reducing the levels of IL8, MIP-3α, and GRO-α (Liu et al., 2010), suggesting that this miRNA plays an essential role in the control of the inflammatory response to *H. pylori* and possibly in the limitation of tissue damage observed in patients with gastritis and gastric cancer. In addition, hsa-miR-146a also regulates the expression of the PTGS2 gene (Liu et al., 2012b), which produces prostaglandin E2 that has been associated with *H. pylori* infection and concomitant infiltration of inflammatory cells to the gastric mucosa (Fu et al., 1999; McCarthy et al., 1999). As a quick reference, the association of several miRNA with *H. pylori* infection, gastritis, and gastric cancer is shown in a summarized way in Table 1.

**miRNA AND GASTRIC INFLAMMATORY STAGES**

*Helicobacter pylori* infection may last many years without inducing any type of gastric discomfort to its human host. Even though between 1 and 3% of infected people develop gastric cancer (Uemura et al., 2001; Suerbaum and Michetti, 2002; Wroblewski et al., 2010), the majority of infected individuals develop a continuous and progressive chronic inflammatory process initiated by non-atrophic gastritis and followed by multifocal atrophic gastritis, intestinal metaplasia, and dysplasia; the latter is considered the truly precancerous stage of the cascade (Correa et al., 1975; Zabaleta et al., 2006; reviewed in Zabaleta, 2012). The rate of change to more advanced gastric lesions is higher than the rate of regression (Correa et al., 1990). Even though pathological features clearly distinguish between each inflammatory stage, the molecular signatures of these transitions have not being explored and the
Table 1 | Association of several miRNA with gastric lesions, from H. pylori infection to gastric cancer.

| hsa-miR-# | Observation | Reference |
|-----------|-------------|-----------|
| 9, 146a, 155, 650, 96, 204 | Chronic active gastritis (NAG) | Lario et al. (2012) |
| 21, 223, 218, 25 | H. pylori infection, gastric cancer | Li et al. (2012a) |
| 155, 146a | Modulation of IL8, MIP3α, GRO-a, Reduced PTGS2 in H. pylori infection | Liu et al. (2010), Liu et al. (2012b), Xiao et al. (2009) |
| 103, 200b, 200c, 375, 532 let-7 | H. pylori-induced gastric inflammation | Isomoto et al. (2012) |
| | Induced by CagA, accumulation of Ras | Hayashi et al. (2012) |
| 17, 20 21 223 | Reduced in metaplastic and non-metaplastic cancerous glands after H. pylori eradication | Shiotani et al. (2012) |
| 17, 204 | Increased after H. pylori eradication | |
| 155, 584, 1290 | Effect on severity of gastritis and presence of more advanced gastric lesions | Oertli et al. (2011), Zhu et al. (2012) |
| 150 | Increased in gastric cancer tissues; induces cell migration and invasion by reducing the expression of EGR2 | Wu et al. (2010) |

underlying mechanisms are unknown. It has been shown that the level of the pro-inflammatory cytokines IL-1β, IL6, IL8, and TNF-α were positively correlated with the level of chronic gastritis but that correlation disappear in the presence of gastric atrophy and was inverse, for IL6 and IL8, in intestinal metaplasia (Isomoto et al., 2012). Interestingly, the levels of these cytokines were, in general, inversely correlated with the levels of several miRNA in the gastric mucosa. For example, the levels of miRNA let-7b were inversely correlated (~0.59) with IL1B levels (p < 0.005) while hsa-miRNA-103 correlated with IL6 (~0.612, p < 0.005), hsa-miR-375 with IL8 (~0.469, p < 0.05), and hsa-miR-200a with TNFA (~0.606; p < 0.005; Isomoto et al., 2012). A profile of several miRNA was associated with reduction of all inflammatory cytokines, suggesting a common mechanism for the control of the expression of these inflammatory mediators (Isomoto et al., 2012). Interestingly, hsa-miR-155 deficient mice present reduced gastritis when compared to wild type mice (Oertli et al., 2011). These responses are associated with increased numbers of H. pylori CFU in the stomachs of infected hsa-miR-155 deficient mice and reduced CD4+ T-cell response evidenced by low production of IFNγ and IL17 (Oertli et al., 2011). After a long follow-up, mice over expressing hsa-miR-584 and hsa-miR-1290 showed changes associated with gastric intestinal metaplasia including the appearance of colonic epithelium and colonic markers (Muc-2; Zhu et al., 2012), suggesting a role of these two miRNA in the development of more advanced gastric lesions. However, the role played by H. pylori, if any, was not determined in this in vivo follow-up. It is possible that the presence of H. pylori infection may shorten the time for the appearance of the epithelial abnormalities. However, even after eradication of H. pylori with a triple antibiotic treatment (amoxicillin, clarithromycin, and pump inhibitors) for a 7-day period, the levels of known oncogenic miRNA, including hsa-miR-21, hsa-miR-25, and hsa-miR-93, did not change (Shiotani et al., 2012). In contrast, the levels of tumor-suppressor miRNA, including let-7 and hsa-miR-204, increased after eradication (Shiotani et al., 2012). These results suggest that after infection and eradication of H. pylori, some underlying processes may continue that promote tissue damage and lead to gastric malignancy. In addition, it is also suggested that more than a single isolated response, the articulated and balanced reaction to the infection and to the inflammatory process dictates the outcome of the cascade initiated by the H. pylori infection. In addition to the inflammatory cascade associated with the development of gastric adenocarcinoma, several miRNA have been linked to H. pylori-induced mucosal associated lymphoid tissue (MALT) lymphomas. Using an array of 376 miRNA (Thorns et al., 2012) found 41 miRNA associated with changes from normal gastric mucosa to gastritis and to MALT. Interestingly, the levels of some of these miRNA seem to change in response to the infiltration of lymphocytes or the presence of H. pylori while only a few (hsa-miR-150, hsa-miR-550, hsa-miR-124a, hsa-miR-518b, and hsa-miR-539) were associated with lymphoma and presented a steady increase from gastritis to MALT (Thorns et al., 2012). Taken together these results suggest that miRNA may be modulating pathways associated with differential outcomes in response to a common trigger, infection with H. pylori. This supports the concept about universality of the miRNA responses and opens up the possibility of more efficacious and global treatments for illnesses with common origins.

miRNA AND GASTRIC CANCER

It has been shown that the distribution of miRNAs on the human genome is non-random but rather, a significant fraction of them are located on chromosomal regions known as “fragile sites” and on genomic regions associated with cancer (Calin et al., 2004). In fact, according to the same report, the incidence of miRNA in these fragile sites is more than ninefold higher than in “non-fragile” regions (Calin et al., 2004). Due to their ability to interact with mRNA, a single miRNA can act as either tumor-suppressors or oncogenes, meaning that a miRNA can be classified as tumor-suppressor- or onco-miRNA, depending on the context of their expression, as has been shown for the miRNA cluster mir-17-92 (He et al., 2005; O’Donnell et al., 2005). Over expression of onco-miRNAs may target certain tumor-suppressor genes and allow the activity of oncogenes and their targets. On the contrary, over expression of tumor-suppressor miRNA would limit the transcription of genes associated with tumorigenesis, cell division, migration and invasion, and metastasis. In this sense, for example, it has been shown that hsa-miR-135a promotes metastasis in breast cancer cell lines by direct interaction with HOX A10 gene, which acts as a metastasis suppressor in this cancer model (Chu...
miRNA AND ITS ROLE AS BIOMARKERS AND PREDICTORS OF GASTRIC CANCER

Compared with the much higher number of mRNA, about 1,000 miRNA have been validated in humans, making feasible the generation of genetic profiles, with microarrays and high throughput sequencing, to associate with disease and disease outcome, or to identify possible biomarkers. In addition, due to its size, miRNA are very stable in biological fluids facilitating the profiling with non-invasive methods. After creating miRNA profiles in gastric cancer, colorectal cancer, and healthy controls, 7 miRNA were identified as specific for gastric cancer (Liu et al., 2012a). However, after validating these 7 miRNA in an independent set of samples, miR-187*, miR-371-5p, and miR-378 remained significantly associated with gastric cancer serum samples (Liu et al., 2012a). Further analysis revealed that hsa-miR-378 had a better biomarker potential and this was corroborated by showing that the level of hsa-miR-378 started to increase very early during the cancer development making it a possible early detection marker for gastric cancer (Liu et al., 2012a). Additional studies have identified several other miRNA that could serve as biomarkers and predictors of gastric cancer (Liu et al., 2011; Li et al., 2012a; Song et al., 2012). The differences observed in the profiles may be related to several things, including ancestry, density of the platform used for the profiling (i.e., microarray, TaqMan arrays), which may allow for lower or higher input of sequences and therefore, limit the probability of identifying specific miRNA. Whatever the technology used, it is clear that miRNA profiling is a potent tool that can be used to improve both diagnosis and prognosis in gastric cancer. The current knowledge of the miRNA role in the pathogenesis of gastric cancer make these as potential targets to either improve therapeutic options currently in use, or to devise new strategies for the treatment of the disease. These treatments have to be directed to at least two things, to reduce the malignant process that lead to hyper-proliferation of gastric cells and are associated to malignant transformation, and to reduce the inflammatory response that promote the influx of immune cells into the gastric mucosa. In addition, it is very possible that H. pylori has its own set of miRNA that can affect the immune response of the host in order to increase the chances of perpetuating its infection.

CONCLUSION

microRNA profiles have been established, and most probably will be used as molecular targets to modify the interaction of H. pylori with gastric cells and to reduce the inflammation and cellular malignancy that may lead to gastric cancer. Among profiles of mRNA, methylation (cpG), genome wide association studies (GWAS), miRNA profiles have the highest potential to successfully become widely used to reach the goal of “personalized medicine” by which, a patient is to be medically treated according to his/her...
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