EUR. J. ONCOL., vol. 19, Suppl n. 1, pp. 8-10, 2014 

# MicroRNA

*Annarosa Arcangeli*[1], *Gianluca Bartoli*[1], *Elisa Giommoni*[2]

[1] Department of Experimental and Clinical Medicine, Section of Internal Medicine, University of Florence; [2] Medical Oncology Unit, Dpt of Oncology, Azienda Ospedaliera Universitaria Careggi, Florence, Italy

MicroRNAs (miRNAs) are small (~22 nucleotides) non-coding RNAs, which regulate gene expression at the post-transcriptional level, through the binding to complementary sites of target mRNAs in the 3'-untraslated (3'UTR) regions. By this way, miRNAs lead to either degradation of target mRNAs or repression of mRNA translation. On the whole, miRNAs exert an essential contribution to the regulation of the encoding genome, finely tuning gene expression (1). By controlling gene expression, miRNAs contribute to regulate diverse biological processes, such as stem cell maintenance, development, cell metabolism, proliferation, differentiation and apoptosis (2). Moreover, increasing evidence indicates that the deregulation of some specific miRNAs is an hallmark of human cancer (3). The aberrant expression of selected miRNAs in several cancer types does not represent just a random association, but plays a causal role in different steps of the tumorigenic process, from the initiation and development to progression toward the acquisition of a metastatic phenotype. Depending on the target RNA they affect, some miRNAs can act as oncogenes whereas other behave as tumor suppressors. In general terms, those miRNAs which are upregulated in cancers exert an oncogenic effect, and viceversa. Finally, some miRNAs possess the tumor marker potential for diagnostic, therapeutic, prognostic exploration (3).

In the present review we provide a brief overview of the miRNAs aberrantly expressed in cancers of the gastro intestinal (GI) tract, with an insight at the possible implications from a clinical point of view. We will focus to either miRNAs whose expression is dysregulated at the tissue (tumoral) level, or to those specifically detected in the serum. The latter are acquiring an even better validity for cancer early detection.

***Esophageal carcinoma (EC)***: Several works investigated the alterations of miRNAs in either esophageal squamous cell carcinoma (ESCC) or in esophageal adenocarcinoma (EAC), as well as in its precursor lesion, the Barrett esophagus (BE). Several dysregulated miRNAs, as well as their target genes have been identified, and the functional roles of many miRNAs in the tumorigenesis of EC have been characterized. As an example, miR-21 expression turned out to be upregulated in EAC, behaving as a negative regulator of (PDCD4), a well known tumor suppressor gene, thus playing an oncogenic role in both EAC and ESCC (4). On the contrary, miR-200 family members have been found to be downregulated in EAC compared with BE, suggesting their potential role of tumor suppressor miRNA (4). An upregulation of miR-25 and miR-92a in ESCC has been reported. Both miRNAs target CDH1, a fact that suggest a role of these miRNAs in promoting migration and invasion through the reduced expression of E-cadherin. Indeed miR-25 and miR-92a expression is associated with poor prognosis (4). The serum miRNA profile of patients with ESCC has been studied, and seven miRNAs (miR-10a, 22, 100, 148b, 223, 133a, and 127-3p) have been identified as ESCC biomarkers (4). Oncogenic miRNAs (miR-21/miR-184/miR-221) and one tumour suppressor miRNA (miR-375) have been studied in the plasma of 50 patients with ESCC: the plasma level of miR-

21 was higher, while that of miR-375 was significantly lower in ESCC patients compared with controls (5).

*Gastric Cancer (GC)*: several investigators have reported an upregulation of miR-21 and of miR-196a/196b in GC, the latter two miRNAs being over expressed both in the tumor tissues and in the serum of gastric cancer patients (4) The overexpression of miR-370 has been shown to drive the downregulation of TGFBR2, whereas miR-126 overexpression leads to inhibition of SOX2, which seems to contribute to GC carcinogenesis (4). MiR-181b and miR-182 were both significantly downregulated in human GC, and they may function as a tumor suppressor through negative regulation of CREB1 (4). Interestingly, miR-137, which is a negative regulator of CDC42, was downregulated in GC as a result of hypermethylation (4). Liu and colleagues have also investigated the serum miRNA profiles of patients with GC using Solexa sequencing. Among 19 candidate miRNAs, they identified 5 serum miRNAs (miR-1, -20a, -27a, -34, and 423-5p) as biomarkers for GC detection and found also that their expression level was correlated with the tumour stage (6).

*Colorectal cancer (CRC):* besides miR-143 and miR-145, which have been found to have tumor suppressive functions (7), other microRNAs have been found to be altered in CRC in multiple reports, including let-7, miR-34, miR-342, miR-345, miR-9, miR-129, and miR-137 which are frequently hypermethylated in CRC, a fact which accounts for their reduced expression (5). Ng and colleagues found that miR-17-3p and miR- 92a were elevated in the plasma samples of CRC patients and reduced in postoperative samples compared with preoperative ones (5). Wang and his group analyzed the serum expression levels of three miRNAs (miR-17-3p, -29a, and -92a) in nonmetastatic and metastatic CRC patients and found that serum miR-29a had the potential to be a noninvasive biomarker for the early detection of liver metastasis in CRC patients (7). Conversely, Lou and colleagues found that miR-625 was downregulated in CRC and associated with tumour metastasis and poor prognosis (8).

*Pancreatic cancer (PC):* more then one hundred miRNA have been found to be dysregulated in PC. Many of them (miR-221, miR-424, miR-301, miR-100, miR-376a, miR-125b-1, miR-21, miR-16-1, miR-181a,c, miR-92-1, miR-15b, miR-155, let-7f-1, miR-212, miR-107, miR-24-1,2, and let-7d) are upregulated. The most downregulated miRNAs in PC are miR-345, miR-142-P, and miR-139 (9). Szafranska et al., found that the aberrant expression of two particular miRNAs, miR-217 and miR-196a, could distinguish PDAC from normal pancreas and pancreatitis (9). In a similar study, Bloomston et al., demonstrated that the upregulation of miR-155, miR-181a,b,c,d, miR-21, and miR-221 and the downregulation of other miRNAs, including miR-148a,b and miR-375, could differentiate PC from normal tissue and pancreatitis tissue samples (9). The serum levels of four candidate miRNAs (miR-21, -155, -196a, and -210) which had been implicated in PC development turned out to be statistically higher in PC patients compared with the controls (10). Li et al., identified two members of the miR-200 family (miR-200a and -200b) to be overexpressed in PC cancers: both were significantly elevated in the sera of PC and chronic pancreatitis (CP) patients compared with healthy controls (11). Another study found that the serum levels of seven miRNAs (miR-16, -21, -155, -181a, -181b, -196b, and -210) were significantly higher in PC patients compared with CP patients and healthy controls. The Authors concluded that the combination of miR-16, miR-196a with the conventional serum marker CA19-9 was most effective in discriminating PC from non-PC and CP patients (12). Kawaguchi et al., found that the evaluation of the miR-221/miR-375 ratio could be useful for diagnostic purposes. Serum miR-221 concentration was significantly reduced in postoperative samples, whereas high serum levels significantly correlated with distant metastasis, and non-resectable status (13). Finally, in a cohort of 70 patients, the high expression of miR-21 and miR-31 and the low expression of miR-375 were associated with poor overall survival following resection, independent of clinical covariates (14).

*Hepatocellular carcinoma (HCC)*: The expression of miR-199a, miR-92, miR-106a, miR-222, miR-17-

5p, miR-18, and miR-20 was found to correlate with the degree of HCC differentiation, suggesting the involvement of specific miRNAs in the progression of the disease (15). Extensive data showed that particular miRNAs (miR-223, miR-122, miR-101, and miR199-a-5p), commonly associated with cell growth inhibition, are downregulated in HCC and play a role in its progression and the onset of metastatic disease (16). On the contrary miR-96, miR-21, miR-224, miR-221, miR-222 and miR-34a, which are associated with increased cell growth are upregulated in HCC (16). miR-500, identified as an oncofetal miRNA in HCC, displayed an increase concentration in 3 out of 10 HCC patients and its levels were significantly reduced after curative surgery (17). Another study reported serum miRNA profile in a large cohort of HCC patients; the miRNA panel they identified could differentiate HCC patients from healthy controls, chronic hepatitis B patients and cirrhosis patients, and could be a promising marker for the early diagnosis of HCC (18).

## References


1. Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. Science 2001; 294: 853-8.
2. Marson A, Levine SS, Cole MF, *et al*. Connecting microRNA genes to the core transcriptional regulatory circuitry of embryonic stem cells. Cell 2008; 134: 521-33.
3. Iorio VM, Croce CM. Causes and consequences of microRNA dysregulation. Cancer J 2012; 18: 215-22.
4. Song S, Ajani JA. The role of microRNAs in cancers of the upper gastrointestinal tract. Nat Rev Gastroenterol Hepatol 2013; 10 (2): 109-18.
5. Komatsu S, Ichikawa D, Takeshita H, *et al*. Prognostic impact of circulating miR-21 and miR-375 in plasma of patients with esophageal squamous cell carcinoma. Expert Opin Biol Ther 2012; 12 Suppl 1: S53-9.
6. Liu R, Zhang C, Hu Z, *et al*. A five-microRNA signature identified from genome-wide serum microRNA expression profiling serves as a fingerprint for gastric cancer diagnosis. Eur J Cancer 2011; 47 (5): 784-91.
7. Schetter AJ, Okayama H, Harris CC The role of microRNAs in colorectal cancer. Cancer J 2012; 18 (3): 244-52.
8. Lou X, Qi X, Zhang Y, *et al*. Decreased expression of microRNA-625 is associated with tumor metastasis and poor prognosis in patients with colorectal cancer. J Surg Oncol 2013; 108 (4): 230-5.
9. Li W, Lebrun DG, Li M. The expression and functions of microRNAs in pancreatic adenocarcinoma and hepatocellular carcinoma. Chin J Cancer 2011; 30 (8): 540-50.
10. Wang J, Chen J, Chang P, *et al*. MicroRNAs in plasma of pancreatic ductal adenocarcinoma patients as novel blood-based biomarkers of disease. Cancer Prev Res (Phila) 2009; 2 (9): 807-13.
11. Li A, Omura N, Hong SM, *et al*. Pancreatic cancers epigenetically silence SIP1 and hypomethylate and overexpress miR-200a/200b in association with elevated circulating miR-200a and miR-200b levels. Cancer Res 2010; 70 (13): 5226-37.
12. Liu J, Gao J, Du Y, *et al*. Combination of plasma microRNAs with serum CA19-9 for early detection of pancreatic cancer. Int J Cancer 2012; 131 (3): 683-91.
13. Kawaguchi T, Komatsu S, Ichikawa D, *et al*. Clinical impact of circulating miR-221 in plasma of patients with pancreatic cancer. Br J Cancer 2013; 108 (2): 361-9.
14. Ma MZ, Kong X, Weng MZ, *et al*. Candidate microRNA biomarkers of pancreatic ductal adenocarcinoma: meta-analysis, experimental validation and clinical significance. J Exp Clin Cancer Res 2013; 32 (1): 71.
15. Murakami Y, Yasuda T, Saigo K, *et al*. Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and non-tumorous tissues. Oncogene 2006; 25: 2537-45.
16. Li W, Xie L, He X, *et al*. Diagnostic and prognostic implications of microRNAs in human hepatocellular carcinoma. Int J Cancer 2008; 123 (7): 1616-22.
17. Yamamoto Y, Kosaka N, Tanaka M, *et al*. MicroRNA-500 as a potential diagnostic marker for hepatocellular carcinoma. Biomarkers 2009; 14 (7): 529-38.
18. Zhou J, Yu L, Gao X, Hu J, *et al*. Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma. J Clin Oncol 2011; 29 (36): 4781-8.