Decreased expression of microRNA-192 correlates with tumor progression and poor prognosis in patients with colorectal cancer

Baozhen Shan1,2, Pu Chen3, Shengbao Li2, Liu Xu2, Honggang Yu1

1Department of Gastroenterology, Renmin Hospital of Wuhan University, Wuhan, China; 2Department of Gastroenterology, Shiyan Taihe Hospital, Hubei University of Medicine, Hubei, China; 3Department of School of Humanities and Social Science, Hubei University of Medicine, Hubei, China

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Abstract: MicroRNAs, a class of small non-coding RNAs, are involved in pathogenesis of several cancers, including colorectal cancers (CRC). MicroRNA (miR)-192 has been reported to play an important role in controlling biological behaviors, such as cell proliferation and apoptosis. The aim of this study was to investigate the correlations of the tissue expression of miR-192 with clinicopathological characteristics and prognosis in patients with CRC. Colorectal cancer tissues and adjacent tissues were collected from 89 patients with primary CRC during surgery, while normal colorectal tissues were obtained from 30 healthy volunteers during endoscopy. MiR-192 expression of these samples was assessed by quantitative real-time PCR. Kaplan-Meier survival curve was plotted to analyze the association of miR-192 expression with overall survival (OS), and univariate and multivariate logistic regression analysis were performed to further investigate the independent risks for OS. The level of miR-192 was significantly decreased in colorectal cancer tissues compared with that in adjacent tissues (P<0.001), and normal tissues (P<0.001). Level of miR-192 was found to be negatively correlated with tumor size (P=0.001), lymph node metastasis (P<0.018), and distant metastasis (P<0.041). Patients with high miR-192 level showed higher OS than patients with low miR-192 level (P=0.014). Low MiR-192 expression (P=0.017), poorly histology (P=0.035), T classification (T3/T4) (P=0.006), lymph node metastasis (P<0.001), distant metastasis (P=0.013) and TNM stage (III/IV) (P=0.003) were predictive risk factors for OS by univariate analysis. However, only low miR-192 expression (P=0.033), lymph node metastasis (P=0.003) and distant metastasis (P=0.043) were independent risks for OS in patients with CRC by multivariate analysis. Our data indicated that down-regulation of miR-192, which correlates with tumor size, lymph node metastasis, and distant metastasis, was an independent risk for OS in CRC. MiR-192 might be a favorable prognostic biomarker in CRC.

Keywords: MiR-129, CRC, prognosis, OS

Introduction

Colorectal cancer (CRC), which had a low incidence several decades ago, has become one of the leading causes of death from cancer worldwide [1, 2]. Although new approaches to managing CRC have emerged, the main treatment is still surgical resection, combined with radiotherapy and chemotherapy [2]. Besides, the prognosis of CRC is partly dependent on tumor progression [2]. Hence, identifying useful biomarkers to detect tumor progression and predict clinical outcome after curative surgery is urgent needed.

MicroRNAs (miRs), which consist of approximately 22 base pairs, are a family of small non-coding RNA molecules, and regulate target gene expression by binding to 3’ untranslated regulations (UTRs) [3, 4]. As reported, miRs are emerging to be involved in various biological behaviors, such as differentiation, proliferation, apoptosis, migration, leading to be key regulators in various pathogenesis and progression of different diseases, especially cancers [5-7]. Moreover, accumulating data have shown that miRs are promising biomarkers of diagnosis, and prognosis in different kinds of cancers. To data, a large number of dysregulated expres-
Previous studies have reported that miR-192 is significantly decreased in CRC tissues, and involved in cell proliferation, apoptosis, and liver metastasis [11, 12]. In this study, the miR-192 level in colorectal cancer tissues and adjacent tissues of CRC patients was measured, clinico-pathological characteristics were collected, and overall survival (OS) was acquired. The aim of this study was to investigate the correlations of the tissue expression of miR-192 with clinico-pathological characteristics and OS in patients with CRC.

Materials and methods

Patients and tissue samples

89 patients with primary CRC, who did not receive preoperative radiotherapy or chemotherapy, underwent colorectal surgery at department of General Gastroenterology, Renmin Hospital of Wuhan University and Shiyan Taihe Hospital of Hubei University of Medicine, China, from December 2009 to December 2010, were enrolled in this study. The diagnoses of CRC were based on clinical characteristics, radiological findings and pathological confirmation. Patients with tumors associated with Familial Adenomatous Polyposis or inflammatory bowel disease were excluded in this study. Besides, 30 age and gender matched healthy volunteers, who took endoscopic examination, were also enrolled in this study. All the patients and healthy volunteers provided their written consent, and this study was approved by the Ethics Review Board of both Renmin Hospital and Shiyan Taihe Hospital.

Paired tumor tissues and adjacent tissues (>5 cm from tumor tissues) from CRC patients, as well as normal colonic tissues from healthy volunteers were obtained. Meanwhile, clinico-pathological characteristics were collected, including age, gender, histology, tumor location, tumor size, lymphatic invasion, venous invasion, T classification, lymph node metastasis, distant metastasis, TNM stage and OS.

All patients enrolled in this study had been followed up 4 times a year in the first year after surgery, 2 times in the second year, and once a year from third year to the fifth year, and the date of latest follow-up was December 31, 2015. OS was calculated in months from the initial diagnosis to the time of death due to any causes or last data of follow-up.

Analysis of miR-192 expression

Total RNA was extracted from CRC and normal tissues using TRizol regent (Invitrogen), and a NanoVue spectrophotometer was used to assess the concentration and purity of RNA. RNA was then subjected to reverse transcription with One Step PrimerScript miRNA cDNA Synthesis Kit (Takara) according to the manufacturer’s instructions. Quantitative analysis of miR-192 expression was performed using SYBR Premix Ex TaqTM II (Takara), and the miR-192 data were normalized for the expression of U6 and were calculated utilizing the $2^{-\Delta\Delta C_t}$ method [13]. The primers of miR-129 and U6 were listed as follows: miR-192 (Forward: CTGACCTATGAATTGACAGCCA; Reverse: GCTGTCAACGATACGCTACGT); U6 (Forward: CGCTTCGGCAGCACATATAC; Reverse: TTCACGAATTTGCTGTCAT).

Statistical analysis

Wilcoxon signed-rank sum test or Wilcoxon rank sum test was performed to compare the level of miR192 between different groups. The chi-square test or Wilcoxon rank sum test was used to measure the miR-192 levels in CRC patients with different characteristics. Kaplan-Meier curve and Log-rank test were established to analyze OS in different groups. The influence of each variable on OS was measured by univariate and multivariate Cox’s proportional hazards regression. All statistical analyses were performed using SPSS software, Version 19, and $P<0.05$ was considered as a statistically significant difference.

Results

Patient characteristics

Demographic and clinico-pathological characteristics of patients with CRC were shown in Table 1. Of all enrolled CRC patients, there were 36 (40%) patients in age ≤60 and 53 (60%) patients in age >60, with 37 (42%) females and 52 (58%) males. As to histology of tumor, 57 (64%) were well/moderately different-
was 35 (39%), and ≤50 mm was 54 (61%), while 47 (53%) tumors were located in colon, and 42 (47%) were in rectum. Besides, patients with positive lymphatic invasion and venous invasion were 68 (76%), and 37 (42%), respectively. As to metastasis, 44 (49%) were positive lymph node metastasis, 18 (20%) were positive distant metastasis. According to T classification, the number of patients with T1/T2 was 36 (40%), and T3/T4 was 53 (60%), while 21 (24%), 21 (24%), 28 (31%), and 19 (21%) subjects were ranked as I, II, III, IV on the basis of TNM stage.

Expression of miR-192 in colorectal cancer tissues, adjacent tissues and normal tissues

To examine the different expression of miR-192 among colorectal cancer tissues, adjacent tissues from CRC patients and normal tissues from healthy donors, qRT-PCR was performed. As shown in Figure 1, the level of miR-192 (0.185 (0.097-0.243)) was found to be significantly lower in colorectal cancer tissues than

Table 1. Correlations of tissue miR-192 level with demographic and clinicopathological characteristics of patients with colorectal cancer (n=89)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Counts (%)</th>
<th>miR-192 (Median)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≤60</td>
<td>36 (40%)</td>
<td>0.167 (0.079-0.307)</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>53 (60%)</td>
<td>0.187 (0.112-0.221)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>37 (52%)</td>
<td>0.191 (0.098-0.227)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>52 (58%)</td>
<td>0.184 (0.087-0.272)</td>
</tr>
<tr>
<td>Histology</td>
<td>Well/moderately</td>
<td>57 (64%)</td>
<td>0.191 (0.098-0.227)</td>
</tr>
<tr>
<td></td>
<td>Poorly differentiated</td>
<td>32 (36%)</td>
<td>0.184 (0.087-0.272)</td>
</tr>
<tr>
<td>Tumor location</td>
<td>Colon</td>
<td>47 (53%)</td>
<td>0.183 (0.108-0.278)</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>42 (47%)</td>
<td>0.179 (0.083-0.223)</td>
</tr>
<tr>
<td>Tumor size</td>
<td>≤50 mm</td>
<td>54 (61%)</td>
<td>0.212 (0.124-0.313)</td>
</tr>
<tr>
<td></td>
<td>&gt;50 mm</td>
<td>35 (39%)</td>
<td>0.118 (0.076-0.191)</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>Negative</td>
<td>21 (24%)</td>
<td>0.187 (0.087-0.227)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>68 (76%)</td>
<td>0.184 (0.093-0.272)</td>
</tr>
<tr>
<td>Venous invasion</td>
<td>Negative</td>
<td>52 (58%)</td>
<td>0.184 (0.085-0.272)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>52 (58%)</td>
<td>0.184 (0.085-0.272)</td>
</tr>
<tr>
<td>T classification</td>
<td>T1/T2</td>
<td>36 (40%)</td>
<td>0.202 (0.133-0.296)</td>
</tr>
<tr>
<td></td>
<td>T3/T4</td>
<td>53 (60%)</td>
<td>0.156 (0.084-0.219)</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>Negative</td>
<td>45 (51%)</td>
<td>0.211 (0.131-0.311)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>44 (49%)</td>
<td>0.130 (0.080-0.214)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>Negative</td>
<td>71 (80%)</td>
<td>0.201 (0.114-0.296)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>18 (20%)</td>
<td>0.128 (0.071-0.192)</td>
</tr>
<tr>
<td>TNM stage</td>
<td>I</td>
<td>21 (24%)</td>
<td>0.214 (0.113-0.300)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>21 (24%)</td>
<td>0.203 (0.109-0.312)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>28 (31%)</td>
<td>0.180 (0.109-0.221)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>19 (21%)</td>
<td>0.121 (0.060-0.185)</td>
</tr>
</tbody>
</table>

Data are presented as counts (%) or median (25th-75th). *A p Value <0.05 was considered statistically significant. Significance of the comparison was determined by chi-square test or Wilcoxon rank sum test.

Figure 1. MiR-192 expressions in colorectal cancer tissues, adjacent tissues and normal tissues. The comparison of difference was performed by Wilcoxon signed-rank sum test or Wilcoxon rank sum test.
that in paired adjacent tissues (0.370 (0.229-0.467), \textit{P}<0.001) and normal tissues (0.404 (0.271-0.527), \textit{P}<0.001), while there was no statistical difference of miR-192 expressions between adjacent tissues and normal tissues (\textit{P}=0.355).

\textit{Correlations of tissue miR-192 level with demographic and clinicopathological characteristics of patients with CRC}

To investigate the potential role of miR-192 in the development and progression of CRC, we then measured the miR-192 levels in CRC patients with different characteristics. As shown in Table 1, we found that significant lower expressions of miR-192 were found in the groups of larger tumor size (>50 mm, 0.118 (0.076-0.191), \textit{P}=0.001), positive node metastasis (0.130 (0.080-0.214), \textit{P}=0.018), and positive distant metastasis (0.128 (0.071-0.192), \textit{P}=0.041), compared with those in the group of smaller tumor size (≤5 cm, 0.212 (0.124-0.313)), negative node metastasis (0.211 (0.131-0.311)) and negative distant metastasis (0.201 (0.114-0.296)), respectively, which indicated that level of miR-192 was negatively correlated with tumor size, lymph node metastasis, and distant metastasis. However, no significant correlations were found between the level of miR-192 and other clinicopathological characteristics (Table 1).

\textit{Association between tissue miR-192 level and OS}

Since OS has been considered as an important indicator of prognosis, we then further investigated whether the level of miR-192 was associated with OS. According to the median value of miR-192 expression in colorectal cancer tissues, we divided CRC patients into high level group (>0.185, \textit{n}=44) and low level group (≤0.185, \textit{n}=45). Meanwhile, Kaplan-Meier curve and Log-rank test were performed to analyze the difference of OS in these two groups of CRC patients. We found that groups with high miR-192 level showed significant higher OS than groups with low miR-192 level (Figure 2, \textit{P}=0.014), which indicated that miR-192 level was associated with prognosis.

In order to further investigate the role of miR-192 in prognosis, univariate Cox’s and multivariate Cox’s proportional hazards regression model were performed. Low level of miR-192 (\textit{P}=0.017, HR=1.825, 95% CI: 1.114-2.988), poorly differentiated group (histology) (\textit{P}=0.035, HR=1.715, 95% CI: 1.040-2.827), higher grade of T classification (T3/T4) (\textit{P}=0.006, HR=2.064, 95% CI: 1.230-3.464), positive lymph node metastasis (\textit{P}=0.001, HR=2.721, 95% CI: 1.308-4.484), positive distant metastasis (\textit{P}=0.013, HR=2.035, 95% CI: 1.633-3.560) and advanced TNM stage (III/IV) (\textit{P}=0.003, HR=2.213, 95% CI: 1.292-3.520) were found to be important risky predictors for OS of CRC patients in univariate model (Table 2), while only low miR-192 expression (\textit{P}=0.033, HR=1.834, 95% CI: 1.050-3.204), lymph node metastasis positive (\textit{P}=0.003, HR=2.259, 95% CI: 1.308-3.904) and distant metastasis positive (\textit{P}=0.043, HR=1.892, 95% CI: 1.021-3.506) were inde-
Considering that many miRs, including miR-192, have been found to be dysregulated in CRC, and miR-192 is a key mediator in controlling cell proliferation, apoptosis, and liver metastasis in CRC, miR-192 was selected as a candidate biomarker to predict tumor progression and clinical outcome in our study. Firstly, we assessed the different expression of miR-192 in cancer tissues, adjacent-tumor tissues from CRC patients, and normal tissues from healthy donors. We found that the level of miR-192 was markedly decreased in cancer tissues compared with that in adjacent tissues and normal tissues, which is consistent with previous studies [11, 12], while there was no significant difference of miR-192 between adjacent tissues and normal tissues. Although miR-192 has been found to be decreased in colorectal cancer, it is still unclear.

### Table 2. Univariate analyses of factors for predicting poor prognosis in patients with colorectal cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MiR-192 (low vs. high)</td>
<td>1.825</td>
<td>1.114-2.988</td>
<td>0.017*</td>
</tr>
<tr>
<td>Age (&gt;60 vs. ≤60)</td>
<td>1.244</td>
<td>0.750-2.063</td>
<td>0.393</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>1.347</td>
<td>0.817-2.223</td>
<td>0.239</td>
</tr>
<tr>
<td>Histology (poorly vs. moderately/well)</td>
<td>1.715</td>
<td>1.040-2.827</td>
<td>0.035*</td>
</tr>
<tr>
<td>Tumor location (rectum vs. colon)</td>
<td>1.274</td>
<td>0.780-2.082</td>
<td>0.333</td>
</tr>
<tr>
<td>Tumor size (&gt;50 mm vs. ≤50 mm)</td>
<td>1.538</td>
<td>0.939-2.519</td>
<td>0.087</td>
</tr>
<tr>
<td>Lymphatic invasion (positive vs. negative)</td>
<td>1.188</td>
<td>0.666-2.118</td>
<td>0.559</td>
</tr>
<tr>
<td>Venous invasion (positive vs. negative)</td>
<td>1.237</td>
<td>0.754-2.030</td>
<td>0.399</td>
</tr>
<tr>
<td>T classification (T3/T4 vs. T1/T2)</td>
<td>2.064</td>
<td>1.230-3.464</td>
<td>0.006*</td>
</tr>
<tr>
<td>Lymph node metastasis (positive vs. negative)</td>
<td>2.721</td>
<td>1.651-4.484</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Distant metastasis (positive vs. negative)</td>
<td>2.035</td>
<td>1.163-3.560</td>
<td>0.013*</td>
</tr>
<tr>
<td>TNM stage (III/IV vs. I/II)</td>
<td>2.213</td>
<td>1.292-3.520</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

*A p value <0.05 was considered statistically significant. Significance was determined by univariate Cox's proportional hazards regression analysis.

### Table 3. Multivariate analyses of factors for predicting poor prognosis in patients with colorectal cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MiR-192 (low vs. high)</td>
<td>1.834</td>
<td>1.050-3.204</td>
<td>0.033*</td>
</tr>
<tr>
<td>Histology (poorly vs. moderately/well)</td>
<td>1.422</td>
<td>0.823-2.455</td>
<td>0.207</td>
</tr>
<tr>
<td>T classification (T3/T4 vs. T1/T2)</td>
<td>1.302</td>
<td>0.748-2.266</td>
<td>0.351</td>
</tr>
<tr>
<td>Lymph node metastasis (positive vs. negative)</td>
<td>2.259</td>
<td>1.308-3.904</td>
<td>0.003*</td>
</tr>
<tr>
<td>Distant metastasis (positive vs. negative)</td>
<td>1.892</td>
<td>1.021-3.506</td>
<td>0.043*</td>
</tr>
<tr>
<td>TNM stage (III/IV vs. I/II)</td>
<td>1.380</td>
<td>0.799-2.381</td>
<td>0.248</td>
</tr>
</tbody>
</table>

*A p value <0.05 was considered statistically significant. Significance was determined by multivariate Cox’s proportional hazards regression analysis.

Collectively, these data indicated that miR-192 was a favorable prognostic biomarker in CRC.

### Discussion

As one of the leading causes of cancer-related death worldwide, CRC has been facing the difficulties in diagnosis, treatment and prognosis [2]. Recently, accumulating studies have focused on identifying molecular biomarkers to improve precision medicine, thus leading to better diagnosis and clinical outcome [14]. Interestingly, miRs, regulating more than 1/3 of human genes and the majority of pathways, are important mediators involved in cancers, through controlling cell proliferation, apoptosis, metastasis and chemoresistance [7, 14]. Furthermore, multiple miRs are considered to be potential biomarkers in various diseases, including cancers [7, 15-17].

To date, several miRs have been reported to be differentially expressed in CRC tissue, and correlate with clinicopathological characteristics [17]. For example, miR-21 was found to be significantly increased in tumor tissues in CRC, involved in cell proliferation and invasion, and up-regulation of miR-21 was associated with poor prognosis [18, 19]. Until now, miR-192 has been reported to be decreased in different carcinomas, including CRC [20-23]. Besides, several studies have demonstrated that miR-192 was involved in tumor initiation and progression, through regulating its target genes, such as p53, Zeb2, RBI [12, 23, 24].

Considering that many miRs, including miR-192, have been found to be dysregulated in CRC, and miR-192 is a key mediator in controlling cell proliferation, apoptosis, and liver metastasis in CRC, miR-192 was selected as a candidate biomarker to predict tumor progression and clinical outcome in our study. Firstly, we assessed the different expression of miR-192 in cancer tissues, adjacent-tumor tissues from CRC patients, and normal tissues from healthy donors. We found that the level of miR-192 was markedly decreased in cancer tissues compared with that in adjacent tissues and normal tissues, which is consistent with previous studies [11, 12], while there was no significant difference of miR-192 between adjacent tissues and normal tissues.

Although miR-192 has been found to be decreased in colorectal cancer, it is still unclear...
whether tissue miR-192 expression differs in CRC patients with different characteristics. Next, we analyze the correlation between miR-192 tissue level and various clinicopathological characteristics. The data demonstrated that down-regulated expression of miR-192 was associated with larger tumor size, which consistent with previous study [11]. Most importantly, we firstly found that the expression of miR-192 was negatively correlated with lymph node metastasis, distant metastasis, which could be explained by its role in regulating cell invasion [11, 25]. However, no significant correlation of miR-192 expression with other demographic and clinicopathological characteristics, including TNM stage. Previous study showed that miR-192 expression was significantly decreased in stage IV compared with that in stage I or II in CRC patients [12], while no significant difference seen in our study. The discrepancy may be cause by different crowds and analysis methods.

OS has been considered as an important indicator of prognosis, thus we then further investigated whether the level of miR-192 was associated with OS. According to the medium value in CRC tissues, we divided patients into two groups, group of high miR-192 level and group of low miR-192. Patients with high miR-192 level showed higher OS than patients with low miR-192 level measured by Kaplan-Meier curve, which indicated that miR-192 might be a potential biomarker to predict clinical outcome.

In order to further investigate whether miR-192 was an independent risk for OS in CRC patients, univariate Cox's and multivariate Cox's proportional hazards regression analysis were then performed. Interestingly, decreased expression of miR-192 was an independent for OS, which indicated that miR-192 could be a promising molecular useful for prognosis in the future. Besides, as to other variables, poorly differentiated group (histology), higher grade of T classification, positive lymph node metastasis, positive distant metastasis and advanced TNM stage were found to be predictive risks for OS, while only lymph node metastasis and distant metastasis were independent risks for OS in patients with CRC. Lymph node metastasis and distant metastasis have been reported to be independent prognostic factors for CRC patients in previous study [26, 27], which is consistent with the data in this study, indicating that these two factors actually affect prognosis of CRC patients. However, other characteristics, such as vascular invasion, histology grade were reported to be independent risks in other studies [28, 29], while they were not found to be independent predictive factors for CRC patients in this study. Different subjects, diverse statistical survey may account for the differences.

In summary, this study demonstrated three significant findings as followed: Firstly, the expression level of miR-192 was significant lower in tumor tissues than that in adjacent-tumor tissues from CRC patients and normal tissues from healthy controls; secondly, miR-192 tissue level was negatively correlated with tumor size, lymph node metastasis, and distant metastasis; Thirdly, decreased expression of miR-192 was an independent for OS. All the evidence indicated that decreased expression of microRNA-192 correlates with tumor progression and poor prognosis in patients with CRC, and might be a potential therapeutic target for the treatment of CRC.

Disclosure of conflict of interest

None.

Address correspondence to: Honggang Yu, Department of Gastroenterology, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuhan 430060, China. Tel: +86-27-88041911; Fax: +86-27-88041911; E-mail: yhgang818@163.com

References

seed pairing, often flanked by adenosines, in
Lewis BP, Burge CB and Bartel DP. Conserved
366: 489-491.

Mirnezami R, Nicholson J and Darzi A. Prepar

quantitative PCR and the 2(-Delta Delta C(T))
Oncogene 2014; 33: 5332-5340.

Are C, Brattain M and Wang J. MicroRNA-192
Geng L, Chaudhuri A, Talmon G, Wisecarver JL,
566.

and -215 are frequently downregulated in
Zhu J, Xing C and Xu H. microRNA-192, -194

p53-Inducible microRNAs, miR-192 and miR-
nated regulation of cell cycle transcripts by
Linsley PS, Cleary MA and Chau BN. Coordi
Guo J, Chang AN, Jackson AL, Carleton MO,
Georges SA, Biery MC, Kim SY, Schelter JM,
147: 847-859, e811.


Zhu J, Xing C and Xu H. microRNA-192, -194
and -215 are frequently downregulated in

Geng L, Chaudhuri A, Talmon G, Wise-carver JL,
Oncogene 2014; 33: 5332-5340.

Livak KJ and Schmittgen TD. Analysis of rela-
tive gene expression data using real-time quan-

Mimezami R, Nicholson J and Darzi A. Prepar-

Lewis BP, Burge CB and Bartel DP. Conserved
seed pairing, often flanked by adenosines, in-

Calin GA and Croce CM. MicroRNA signatures

Yi R, Li Y, Wang FL, Miao G, Qi RM and Zhao YY.
MicroRNAs as diagnostic and prognostic bio-
markers in colorectal cancer. World J Gastroin-

Asangani IA, Rasheed SA, Nikolova DA, Le-
upold JH, Colburn NH, Post S and Allgayer H. MicroRNA-21 (miR-21) post-transcriptionally
downregulates tumor suppressor Pdc4d and
stimulates invasion, intravasation and metast-
asis in colorectal cancer. Oncogene 2008; 27:
2128-2136.

Schetter AJ, Leung SY, Sohn JJ, Zanetti KA,
Bowman ED, Yanaihara N, Yuen ST, Chan TL,
Kwong DL, Au GK, Liu CG, Calin GA, Croce CM
and Harris CC. MicroRNA expression profiles
associated with prognosis and therapeutic out-
come in colon adenocarcinoma. JAMA 2008;
299: 425-436.

Mathe EA, Nguyen GH, Bowman ED, Zhao Y,
Budhu A, Schetter AJ, Braun R, Reimers M, Ku-
mamoto K, Hughes D, Altorki NK, Cassson AG,
Liu CG, Wang XW, Yanaihara N, Hagiwara N,
Dannenberg AJ, Miyashita M, Croce CM and
Harris CC. MicroRNA expression in squamous
cell carcinoma and adenocarcinoma of the
esophagus: associations with survival. Clin

Jin Z, Selaru FM, Cheng Y, Kan T, Agarwal R,
Mori Y, Olaire AV, Yang J, David S, Hamilton JP,
Abraham JM, Harmon J, Duncan M, Montgomery EA and Meltzer SJ. MicroRNA-192 and
-215 are upregulated in human gastric cancer
in vivo and suppress ALCAM expression in vi-

Yanaihara N, Caplen N, Bowman E, Seike M,
Kumamoto K, Yi M, Stephens RM, Okamoto A,
Yokota J, Tanaka T, Calin GA, Liu CG, Croce CM
and Harris CC. Unique microRNA molecular
profiles in lung cancer diagnosis and progno-

Feng S, Cong S, Zhang X, Bao X, Wang W, Li H,
Wang Z, Wang G, Xu J, Du B, Qu D, Xiong W, Yin
M, Ren X, Wang F, He J and Zhang B. MicroR-
NA-192 targeting retinoblastoma 1 inhibits
cell proliferation and induces cell apoptosis
in lung cancer cells. Nucleic Acids Res 2011;
39: 6669-6678.

Ye M, Zhang J, Zhang J, Miao Q, Yao L and
Zhang J. Curcumin promotes apoptosis by ac-
vulating the p53-miR-192-5p/215-XIAP pathway
2015; 357: 196-205.

Khella HW, Bakhet M, Allo G, Jewett MA, Girgis
AH, Latif A, Girgis H, Von Both I, Bjarnason GA

MiR-192 in CRC


