Genomics xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Genomics

journal homepage: www.elsevier.com/locate/ygeno

Review

Ribonucleic-acid-biomarker candidates for early-phase group detection of common cancers

Elmira Shajari[a], Hamidreza Mollasalehi[b,*]

[a] Protein Research Center, Shahid Beheshti University, G.C., Tehran, Iran
[b] Department of Cellular and Molecular Biology, Shahid Beheshti University, G.C, Tehran 1983969411, Iran

ARTICLE INFO

Keywords:
Cancers screening
Circulating biomarkers
miRNA dysregulation
Non-invasive diagnosis

ABSTRACT

Cancer is considered as a challenging lethal agent around the world and its detection at early stages would help prevention of the high mortality. Among the widely used biomarkers in clinical diagnosis of cancer, extracellular non-coding RNAs as ribonucleic acid biomarkers serve as state-of-the-art candidates for molecular diagnosis. In that regard, microRNAs are of great priority mainly because of high variety and stability in body fluids. Accordingly, common miRNAs among most prevalent cancers could help us (pre)diagnose cancer with high accuracy in target samples. In this study, common lethal cancers to humans were investigated in case of miRNA profiles to determine the possible common correlation between miRNA up-regulation or down-regulation (as a ribonucleic acid biomarker) and developing the cancers. It was shown that among the investigated miRNAs, five typical extracellular miRNAs (miR-18a, miR-21, miR-155, miR-221, and miR-375) dysregulation are predominant in most cancer varieties comprising breast, colon, lung, prostate, pancreas, gastric, ovarian, esophagus and liver. This could serve as an appropriate target site for developing point-of-care approaches for cancer detection e.g. designing diagnostic biosensor-based microarrays or kits for both quantification and qualification of the biomarkers. Besides, the miRNA candidates could be efficiently applied to cancer therapeutic approaches.

1. Introduction

Cancer keeps on being a remarkable cause of worldwide mortality in spite of many years of effort and cost. Deadliest types of cancers to human includes pancreas, liver, lung and bronchus, prostate/breast, colon, rectum and ovary [1–3]. Most of cancers do not induce clinical symptoms until in the later stages when the therapeutic treatment is no longer an option. However, detection of cancer at first stages, regardless of its origin, greatly increases the chance of effective treatments. In spite of much research in cancer biomarkers, only a few are considered for early diagnosis of common cancers. In addition, there is not a general biomarker for population screening in order to detect both asymptomatic cancers and early-staged cancers. Hence, investigating more sensitive and non-invasive biomarkers is still a promising challenge in cancer diagnosis and prognosis [4]. Accessing circulating cancer biomarkers through biological fluids using liquid biopsy seems to propose a promising cost-effective and non-invasive solution. Literally, cf-miRNAs are considered as ideal circulating cancer biomarkers due to their ease of access and quantification, besides integration with other macromolecules e.g. proteins, and high stability in plasma [5, 6]. MiRNAs are endogenous, small (18–24 nt), non-coding (nc) RNA molecules that play important regulatory roles in cell proliferation, apoptosis, metastasis and angiogenesis [7]. Dysregulated miRNA(s) have both oncogenic and tumor-suppressing effects depending on their corresponding targets. The increase or decrease of miRNAs is related to the role of their target genes in cancer progression or regression. MiRNAs are mainly categorized in two groups: 1) OncomiRs that are up-regulated in cancers to target protein-coding transcripts in tumor suppressive pathways, and consequently increase cell proliferation, invasion and metastasis. 2) Tumor-suppressor miRNAs that repress the oncogenic genes and their down-regulation in cancer increases the oncogenic activity [8]. MiRNAs show various expression patterns in tissue and blood of many cancers in comparison with normal samples. Furthermore, miRNA profiles in cancers with various tissue origins are distinct from each other [9]. There are increasing number of reports on determining miRNA dysregulation in specific cancers for improving

Abbreviations: miRNA/miR, microRNA; cf-miRNAs, cell-free microRNAs; DLBCL, diffuse large B-cell lymphoma; AML, acute myeloid leukemia; PUMA, p53 up-regulated modulator of apoptosis; AUC, area under the curve; ESCC, esophageal squamous-cell carcinoma

* Corresponding Author at: Department of Cellular and Molecular Biology, Faculty of Biological Sciences and Technology, Shahid Beheshti University, Velenjak, Tehran, Iran.
E-mail address: H_mollasalehi@sbu.ac.ir (H. Mollasalehi).

https://doi.org/10.1016/j.ygeno.2018.08.011
Received 30 May 2018; Received in revised form 6 August 2018; Accepted 31 August 2018

prognosis, diagnosis and treatment. Among the dysregulations are alterations of miR-195, miR-let7a, miR-182, miR-30a, miR-106b in breast cancer [10-12]; dysregulation of miR-17-3p, miR-92, miR-29c in colorectal cancer [13,14]. In addition, up-regulation of miR-205, miR-93, miR-106b and miR-451 in ovarian cancer [15–17] as well as up-regulation of miR-125b, miR-223, miR-106b in hepatocellular carcinoma [18,19] and also up-regulation of plasma miR-17-5p, miR-20a, miR-378 and miR-199a in gastric cancer [20–22] are highlighted in comparison to healthy controls. MiRNA dysregulation patterns not only provide the opportunity to characterize type and stage of cancers, but also are used as a tool for cancer prognosis, diagnosis and therapy. Lawrie et al. for the first time suggested the diagnostic utility of miRNAs by comparing the expression level of miR-21 and miR-155 in serum of DLBCL patients and healthy controls [23]. More recently, Chen et al. have indicated the higher expression of miR-196a in patients with early gastric adenocarcinoma compared with healthy samples which shows the miR-196a as a biomarker for early detection of gastric cancer [24]. There are many reports determining one or some miRNAs as the biomarker of specific cancers. However, finding common miRNAs among most prevalent and lethal cancers could assist (pre)diagnosis of target samples with high accuracy. MiRNAs show various expression patterns in tissue and blood of cancerous patient. Some dysregulations seem to be common in most cancers possibly due to their principle characteristics in cancer-associated biological processes. The main objective of this study was to investigate miRNA alteration profiles of prevalent cancers to define a combination of miRNAs in which their early-stage dysregulation could serve as a general biomarker for simultaneous diagnosis of most common cancers. Targeting these shared miRNAs among the most prevalent and lethal cancers could assist efficient (pre)diagnosis of common cancers.

2. Common lethal cancers

We obtained comprehensive information on the prevalence, survival, and mortality of cancers with a complete exploration of the published statistics from American cancer society and National Cancer Institute of the United States (NIH). Initially, we determined common lethal cancers with high demand for early detection to increase the survival rate. For this purpose, high-incidence cancers (more than 4 incidences per 100,000 people) were selected. The statistics was obtained from the SEER Cancer Statistics Review releases for the years 1975–2012 [25]. Among all selected common cancers, the ones with 70% or higher survival rate as well as those whose early diagnosis did not significantly affect the survival rate such as thyroid and skin cancers were omitted from the database. It should be noted that while prostate and breast cancers have a survival rate of around 90%, their mortality rate is considerable due to their high incidence. Hence, they are not excluded from the list. The selected cancers with five-year survival rates in early and late-stage diagnosis are listed in Table 1.

3. Investigating miRNA profiling in cancers

Online databases e.g. miRCancer were thoroughly searched for the relevant studies regarding the miRNA dysregulation pattern in selected cancers up to May 2017. The data regarding miRNA changes in human serum, plasma, and blood specimens was extracted while tissue and cell-lines miRNA alterations were excluded. The miRNAs were classified into categories of fifty for ease of comparison. Finally, we selected common dysregulated miRNAs potential of being introduced as general biomarkers.

Complete list of dysregulated serum/plasma miRNA biomarkers in various cancers were prepared according to the mentioned methodology. Among miRNA categories, high overlapping miRNAs in all listed common cancers were selected. Significantly, five miRNAs were determined that at least three of them showed alteration in each listed cancers. Dysregulated miRNAs are composed of miR-21, miR-18a, miR-155, miR-221 and miR-375 (Table 2). Some of the miRNAs have oncogenic role while others may present tumor suppressive function.

Table 1
List of most common and lethal cancers. Five-year survival rates in the leading cancer types in early and late-stage diagnosis are compared. [88].

Cancer		Rate of 5-year survival[a] in early diagnosis (local stage)[b]	Rate of 5-year survival in late stage diagnosis (distant stage)[c]
Lung	SCLC[d]	27.3%	2.8%
	NSCLC[e]	58.7%	4.7%
Breast		98.6%	25.9%
Prostate		99.9%	28.2%
Colon & rectum		90.1%	13.1%
Pancreatic		27.1%	2.2%
Ovarian		92.1%	28.3%
Liver		30.5%	3.1%
Gastric		65.5%	4.5%
Esophagus		40.0%	4.2%

[a] Five year survival rate: Rate of alive people (percentage) five years after detection of cancer.
[b] Local stage: The stage in which cancer is occurred and limited to the place of occurrence without spreading.
[c] Distant stage: The stage in which cancer has spread out to other regions.
[d] SCLC: Small Cell Lung Cancer.
[e] NSCLC: Non-Small Cell Lung Cancer.

4. MiR candidates for early phase group detection

4.1. MiR-21

MiR-21 is one of the most intensively studied miRNAs in cancer development. It is considerably elevated (highly conserved miRNA) in a variety of human neoplastic disorders.

miR-21 has a potential of targeting a number of important tumor suppressor genes and associated with tumor cell invasiveness and resistance to apoptosis [26,27]. Circulating miR-21 have been proposed as a potential diagnostic biomarker in sera of most cancers [28] including lung [29], breast [30,31], prostate [32], colorectal [33], pancreas [34], ovarian [35], liver [36,37], gastric [38], and esophageal [39].

4.2. MiR-155

Along with miR-21, miR-155 is also dysregulated in many cancers. MiR-155 as an oncomiR enhances tumor growth, promotes cell proliferation, inhibits apoptosis and is also elevated in AML and diffuse large B-cell lymphoma (DLBCL) as well as types of solid tumors including lung [40,41], breast [42,43], colon [44], and pancreas [45]. However, contrary to all mentioned cancers, miR-155 acts as an oncosuppressor in some other cancers. Some evidence has shown the miR-155 down-regulation correlates with adhesion, migration and invasion of gastric cancer cells [46]. Moreover, in ovarian cancer, up-regulation of miR-155 has prevented proliferation and invasion of ovarian cancer cells [47].

4.3. MiR-18a

MiR-18a is a unique component of miR-17-92 cluster with six other members: miR-17, miR-19a, miR-19b, miR-20a, and miR-92a. The miR-17/92 cluster is well studied mainly for the potential oncogenic role in various malignant diseases. The oncogenic impact of the miR-17-92 cluster is promoted by participating its members in targeting tumor-suppressive proteins and pathways such as PTEN and TGFβ signaling [48]. Although all miRNAs in miR-17-92 have various oncogenic potential in different cancer pathways, miR-18a shows significant up-regulation in plasma/serum of several cancer patients in comparison to

Table 2
Dysregulation patterns of miRNAs in common lethal cancers in serum, plasma, and blood fluids. The miRNAs were classified in groups of fifty for investigation of the profile status in common lethal cancers.

Cancers/miRNA Nomenclature	1-50	51-100	101-150	151-200	201-250	251->300	Ref.
Lung (NSCLC)[1]	19a- 21↑		125b↑	155↑- 197↑- 182↑- 195↓		375↓	(15-19)
Breast	Let7a,b,g↑- 18b↑- 18a↑- 21↑- 30a↓	92a↑	106b↑- 133a↑- 133b↑	145↑- 155↑- 181a↑- 182↑- 195↑	214↑- 222↑	375↑	(19-29)
Prostate	1↑-18a↑-21↑		141↑		221↑	375↑	(30-32)
Colon & Rectum	18a↑- 19a↑ 19b↑-21↑- 29a↑- 29c	92a↑		155↑	221↑	375↓- 601- 760	(19, 33-37)
Panaceas	18a↑- 34a↑- 21↑- 25↑			155↑	210↑-	375↓	(38-41)
Ovarian	Let7a↓-16↑- 15b↑-21↑- 22↑- 25↑	93↑	106b↑ 141↑ 145↓	155↓- 195↑	205↑- 200a↑ 221↑	451↑	(42, 43) (44)
Liver	18a↑- 21↑↑		106b↑- 122↑- 125b-5p↑		221↑- 223↑	375↓	(45-51)
Gastric	Let7a↓- 16_5p↓ 17↑-17_5p↑ 18a↑- 20a↑- 21↑-		106b↑- 106a↑-	155↓- 199a-3p	221↑	375↓ 376c↑- 378↑- 744↑	(6, 19, 52-58)
Esophageal	9↑- 18a↑- 21↑-25↑		100↓	151↑- 155↑	218↑	375↓	(59, 60)

↑: upregulation
↓: downregulation.
Highlight: Shows miRNAs with overlapping dysregulations in most common cancers
[1]NSCLC: Non-Small Cell Lung Cancer.

other members. MiR-18a is upregulated in breast cancer [49], pancreatic [50], liver [51], colon [13], gastric [52],esophageal [53] (Table 2), as well as head and neck squamous cell carcinoma [54], diffuse large B-cell lymphoma [55], urothelial carcinoma of the bladder [56], nasopharyngeal carcinoma (NPC) [57], and basal cell carcinoma [58] and serous ovarian carcinoma [59].

4.4. MiR-221

Increased expression of miR-221 (an oncogenic miRNA) has been noted in patients comparing with healthy controls in various cancers: prostate [32], colon [60], liver [61], and gastric [62], pancreas [63], ovarian [64] (Table 2); additionally, it increases in NK/T-cell lymphoma, larynx cancer, glioma, and melanoma. The reported targets of miR-221 in most cancers are PTEN, p27kip1, p57kip2, and p53 upregulated modulator of apoptosis (PUMA), which are signaling pathways in controlling cell proliferation and apoptosis [65,66].

4.5. MiR-375

Another top most dysregulated miRNA in common cancers is miR-375 that seems to be a multifunctional miRNA and plays a dual role in developing cancers. In spite of tumor suppressor role of miR-375, some researches show a contradictory role for this miRNA in other tumor types and even in breast and prostate cancers where miR-375 is upregulated [67]. MiR-375 suppresses several main oncogenes like PDK1, YAP1, IGF1R and AEG-1. Moreover it shows prognostics value in breast [68], lung [69] prostate [70], colon [71], liver [72], esophageal [39,73], pancreas [63], gastric [74], head and neck squamous cell carcinomas [75] and squamous cervical cancer [76]. Due to miR-375 dysregulation in most common cancers, it could serve as a reserved biomarker for early-detection of prevalent cancers.

The selected miRNAs are nominated according to their high diagnostic value in various cancers. In that regard, the area under receiver-operating characteristic curve (AUC) was considered as the evaluating index of diagnosis accuracy. For instance, Komatsu et al. reported high concentrations of miR-18a in plasma of pancreatic patients which showed a great value of 0.9369 for AUC [77]. There are many reports confirming the high diagnostic value of this biomarker with an extremely high AUC in ESCC (AUC = 0.9449) and hepatocellular carcinoma (AUC = 0.881) [51,53]. In the meta-analysis conducted by Jin et al. involving 979 cancer patients and 713 healthy controls, they reported the pooled AUC of 0.86 for miR-18a as a promising biomarker for cancer detection [78]. Regarding miR-155 as another diagnostic biomarker, Hu et al. surveyed 25 studies including 1866 cancer patients and 1226 healthy controls and reported the AUC of 0.867, which indicated the high diagnostic accuracy of miR-155 [79]. Recently, a meta-analysis on 645 cancer patient and 241 healthy controls revealed pooled AUC of 0.82 and suggested miR-375 as a potential biomarker for cancer screening [80].

It should be noted that in spite of important diagnostic roles of the selected miRNAs, targeting each individual miRNA separately provides low diagnostic value. Hence, it is the combination of miRNAs that could enhance the sensitivity and specificity of detection approaches. Using the ratio of the concentration of miR-21/miR-375 as a combined biomarker, Komatsu et al. analyzed plasma of 50 ESCC patients and 20 healthy controls and showed the great AUC of 0.816 higher than AUC of each miRNA individually [81]. Likewise, in the study by Kawaguchi et al. on pancreatic cancer, the overall AUC of miR-221, miR-375, and ratio of miR-221/miR-375 were determined as 0.743, 0.573, and 0.762, respectively which shows increased AUC in the combined form [82]. Moreover, Motawi et al. showed that the combined expression of miR-21 and miR-221 could be consider as a prospective breast cancer biomarker [83].

Overall, the identified miRNAs, which are significantly dysregulated in the early stages of the discussed common cancers, could be used in screening, prognosis, diagnosis and cancer gene therapy as well as the development of rapid nucleic acid detection technologies based on previous experiences in our laboratory [84–87].

5. Conclusion

Early detection of cancer sets the stage for timely protection of patients and prevents potential outbreaks. Thus, introducing general biomarkers for screening most common cancers in their early phases could significantly decrease cancer death rates. Therefore, defining a biomarker to be used in non-invasive detection approaches of common cancers with high sensitivity and specificity would pave the way of developing kits for cancer screening. In that regard, circulating miRNA dysregulations have the capacity of being considered as gold biomarkers for the purpose. However, a single miRNA dysregulation might not serve as an efficient biomarker for screening various range of cancers, whereas a combination of miRNA panel would be able to detect most cancers at the early stages. In this study, a panel of miRNAs whose simultaneous measuring could provide a basis for next-generation cancer screening with higher sensitivity and specificity was presented. Up to our knowledge, this is the first report on introducing shared miRNAs as general biomarkers for early screening of common lethal cancers. Accordingly, miRNA profiles of prevalent cancers were investigated and compared to each other to determine frequent dysregulated miRNAs. Our data show that many miRNAs are dysregulated significantly in common cancers including breast, colon, lung, prostate, pancreas, gastric, ovarian, esophagus and liver. Among, five selected miRNAs (miR-21, miR-155, miR-18a, miR-221, and miR-375) are considered suitable to serve as potential diagnostic biomarkers in the prevalent cancers. The nominated miRNAs in cancers play remarkable role in increasing the expression level of oncogenes and silencing the tumor suppressor genes. According to general categorization of miRNAs, oncomiRs (up-regulate in cancers) and tumor-suppressor miRNAs (down-regulate in cancers), increasing evidences show that miR-21, miR-18a and miR-221 act mostly as oncomiR in cancers. However, various studies indicate that miR-155 and miR-375 might have both roles in different cancers. This evidence reveals that combinations of miRNAs are of high diagnostic value and could be considered as gold biomarkers of cancers in detection approaches. The investigation results and selected miRNAs could be advantageous in cancer gene therapy besides prognosis and diagnosis and open up new horizons for future research in order to approach their clinical application.

Acknowledgement

This work was financially supported by National Cancer Control Charity Foundation. The authors also appreciate supports of Shahid Beheshti University.

Conflict of interest

The authors declare that there is no competing financial interest regarding the manuscript content and no conflict of interest.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2016, CA Cancer J. Clin. 66 (1) (2016) 7–30.
[2] M.L. Finkel, Cancer Screening in the Developing World: Case Studies and Strategies from the Field, Dartmouth College Press, 2018.
[3] Organization, W.H, National Cancer Control Programmes: Policies and Managerial Guidelines, World Health Organization, 2002.
[4] R.A. Smith, et al., Cancer screening in the United States, 2015: a review of current American Cancer Society guidelines and current issues in cancer screening, CA Cancer J. Clin. 65 (1) (2015) 30–54.
[5] M.A. Javidi, et al., Cell-free microRNAs as cancer biomarkers: the odyssey of miRNAs through body fluids, Med. Oncol. 31 (12) (2014) 295.
[6] Y. Peng, C.M. Croce, The role of MicroRNAs in human cancer, Signal Transduct.

Target. Therap. 1 (2016) 15004.
[7] J.K. Palanichamy, D.S. Rao, miRNA dysregulation in cancer: towards a mechanistic understanding, Front. Genet. 5 (2014) 54.
[8] J. Lu, et al., MicroRNA expression profiles classify human cancers, Nature 435 (7043) (2005) 834.
[9] P.Y. Wang, et al., Higher expression of circulating miR-182 as a novel biomarker for breast cancer, Oncol. Lett. 6 (6) (2013) 1681–1686.
[10] E.K. Ng, et al., Differential expression of microRNAs in plasma of colorectal cancer patients: a potential marker for colorectal cancer screening, Gut 58 (2009) 1375–1381.
[11] I.-P. Yang, et al., The functional significance of microRNA-29c in patients with colorectal cancer: a potential circulating biomarker for predicting early relapse, PLoS ONE 8 (6) (2013) e66842.
[12] H. Zheng, et al., Plasma miRNAs as diagnostic and prognostic biomarkers for ovarian cancer, PLoS ONE 8 (11) (2013) e77853.
[13] K. Nakamura, et al., Clinical relevance of circulating cell-free microRNAs in ovarian cancer, Mol. Cancer 15 (1) (2016) 48.
[14] T. Ji, et al., Differential microRNA expression by Solexa sequencing in the sera of ovarian cancer patients, Asian Pacific J. Cancer Preven. 15 (4) (2013) 1739–1743.
[15] B.G. Giray, et al., Profiles of serum microRNAs; miR-125b-5p and miR223-3p serve as novel biomarkers for HBV-positive hepatocellular carcinoma, Mol. Biol. Rep. 41 (7) (2014) 4513–4519.
[16] L. Jiang, et al., Plasma microRNA might as a potential biomarker for hepatocellular carcinoma and chronic liver disease screening, Tumor Biol. 36 (9) (2015) 7167–7174.
[17] M. Wang, et al., Circulating miR-17-5p and miR-20a: molecular markers for gastric cancer, Mol. Med. Rep. 5 (6) (2012) 1514–1520.
[18] H. Liu, et al., Genome-wide microRNA profiles identify miR-378 as a serum biomarker for early detection of gastric cancer, Cancer Lett. 316 (2) (2012) 196–203.
[19] C. Li, et al., MiRNA-199a-3p: a potential circulating diagnostic biomarker for early gastric cancer, J. Surg. Oncol. 108 (2) (2013) 89–92.
[20] C.H. Lawrie, et al., Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma, Br. J. Haematol. 141 (5) (2008) 672–675.
[21] T.-H. Chen, et al., Circulating microRNA-196a is an early gastric cancer biomarker, Oncotarget 9 (12) (2018) 10317.
[22] N. Howlader, et al., SEER Cancer Statistics Review, 1975–2012, Based on November 2014 SEER Data Submission, Posted to the SEER Web Site, April 2015, 2015 National Cancer Institute, Bethesda, MD, 2014.
[23] A.M. Krichevsky, G. Gabriely, miR-21: a small multi-faceted RNA, J. Cell. Mol. Med. 13 (1) (2009) 39–53.
[24] S.D. Selcuklu, M.T. Donoghue, C. Spillane, miR-21 as a Key Regulator of Oncogenic Processes, Portland Press Limited, 2009.
[25] B. Wang, Q. Zhang, The expression and clinical significance of circulating microRNA-21 in serum of five solid tumors, J. Cancer Res. Clin. Oncol. 138 (10) (2012) 1659–1666.
[26] J. Wei, et al., Identification of plasma microRNA-21 as a biomarker for early detection and chemosensitivity of non–small cell lung cancer, Chin. J. Cancer 30 (6) (2011) 407.
[27] H. Schwarzenbach, et al., Diagnostic potential of PTEN-targeting miR-214 in the blood of breast cancer patients, Breast Cancer Res. Treat. 134 (3) (2012) 933–941.
[28] M. Chan, et al., Identification of circulating microRNA signatures for breast cancer detection, Clin. Cancer Res. 19 (16) (2013) 4477–4487.
[29] J. Shen, et al., Dysregulation of circulating microRNAs and prediction of aggressive prostate cancer, Prostate 72 (13) (2012) 1469–1477.
[30] Z. Kanaan, et al., Plasma miR-21: a potential diagnostic marker of colorectal cancer, Ann. Surg. 256 (3) (2012) 544–551.
[31] B. Alemar, et al., miRNA-21 and miRNA-34a are potential minimally invasive biomarkers for the diagnosis of pancreatic ductal adenocarcinoma, Pancreas 45 (1) (2016) 84–92.
[32] D.D. Taylor, C. Gercel-Taylor, MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer, Gynecol. Oncol. 110 (1) (2008) 13–21.
[33] J. Xu, et al., Circulating MicroRNAs, miR-21, miR-122, and miR-223, in patients with hepatocellular carcinoma or chronic hepatitis, Mol. Carcinog. 50 (2) (2011) 136–142.
[34] Y. Tomimaru, et al., Circulating microRNA-21 as a novel biomarker for hepatocellular carcinoma, J. Hepatol. 56 (1) (2012) 167–175.
[35] M. Tsujiura, et al., Circulating microRNAs in plasma of patients with gastric cancers, Br. J. Cancer 102 (7) (2010) 1174–1179.
[36] S. Komatsu, et al., Circulating microRNAs in plasma of patients with oesophageal squamous cell carcinoma, Br. J. Cancer 105 (1) (2011) 104–111.
[37] D. Zheng, et al., Plasma microRNAs as novel biomarkers for early detection of lung cancer, Int. J. Clin. Exp. Pathol. 4 (6) (2011) 575–586.
[38] A.A. Abd-El-Fattah, et al., Differential microRNAs expression in serum of patients with lung cancer, pulmonary tuberculosis, and pneumonia, Cell Biochem. Biophys. 67 (3) (2013) 875–884.
[39] Y. Sun, et al., Serum microRNA-155 as a potential biomarker to track disease in breast cancer, PLoS ONE 7 (10) (2012) e47003.
[40] F. Mar-Aguilar, et al., Serum circulating microRNA profiling for identification of potential breast cancer biomarkers, Dis. Markers 34 (3) (2013) 163–169.
[41] Z.-C. Lv, et al., Investigation of microRNA-155 as a serum diagnostic and prognostic biomarker for colorectal cancer, Tumor Biol. 36 (3) (2015) 1619–1625.
[42] N. Habbe, et al., MicroRNA miR-155 is a biomarker of early pancreatic neoplasia, Cancer Biol. Therap. 8 (4) (2009) 340–346.
[43] C.-L. Li, et al., microRNA-155 is downregulated in gastric cancer cells and involved in cell metastasis, Oncol. Rep. 27 (6) (2012) 1960–1966.
[44] W. Qin, et al., MicroRNA-155 is a novel suppressor of ovarian cancer-initiating cells that targets CLDN1, FEBS Lett. 587 (9) (2013) 1434–1439.
[45] C.P. Concepcion, C. Bonetti, A. Ventura, The miR-17-92 family of microRNA clusters in development and disease, Cancer J. (Sudbury, Mass.) 18 (3) (2012) 262.
[46] A.C. Godfrey, et al., Serum microRNA expression as an early marker for breast cancer risk in prospectively collected samples from the Sister Study cohort, Breast Cancer Res. 15 (3) (2013) R42.
[47] R. Morimura, et al., Novel diagnostic value of circulating miR-18a in plasma of patients with pancreatic cancer, Br. J. Cancer 105 (11) (2011) 1733–1740.
[48] L. Li, et al., Serum miR-18a: a potential marker for hepatitis B virus-related hepatocellular carcinoma screening, Dig. Dis. Sci. 57 (11) (2012) 2910–2916.
[49] M. Tsujiura, et al., Circulating miR-18a in plasma contributes to cancer detection and monitoring in patients with gastric cancer, Gastric Cancer 18 (2) (2015) 271–279.
[50] S. Hirajima, et al., Clinical impact of circulating miR-18a in plasma of patients with oesophageal squamous cell carcinoma, Br. J. Cancer 108 (9) (2013) 1822.
[51] S.S. Chang, et al., MicroRNA alterations in head and neck squamous cell carcinoma, Int. J. Cancer 123 (12) (2008) 2791–2797.
[52] A.J. Alencar, et al., MicroRNAs are independent predictors of outcome in diffuse large B-cell lymphoma patients treated with R-CHOP, Clin. Cancer Res. 17 (2011) 4125–4135 (p. clincanres. 0224.2011).
[53] F.A. de la Peña, et al., Loss of p53 and acquisition of angiogenic microRNA profile are insufficient to facilitate progression of bladder urothelial carcinoma in situ to invasive carcinoma, J. Biol. Chem. 286 (23) (2011) 20778–20787.
[54] Z. Luo, et al., miR-18a promotes malignant progression by impairing microRNA biogenesis in nasopharyngeal carcinoma, Carcinogenesis 34 (2) (2012) 415–425.
[55] M. Sand, et al., Expression of microRNAs in basal cell carcinoma, Br. J. Dermatol. 167 (4) (2012) 847–855.
[56] E.J. Nam, et al., MicroRNA expression profiles in serous ovarian carcinoma, Clin. Cancer Res. 14 (9) (2008) 2690–2695.
[57] X.X. Pu, et al., Circulating miR-221 directly amplified from plasma is a potential diagnostic and prognostic marker of colorectal cancer and is correlated with p53 expression, J. Gastroenterol. Hepatol. 25 (10) (2010) 1674–1680.
[58] O. Shaker, et al., miRNA-101-1 and miRNA-221 expressions and their polymorphisms as biomarkers for early diagnosis of hepatocellular carcinoma, Infect. Genet. Evol. 51 (2017) 173–181.
[59] M.-Y. Song, et al., Identification of serum microRNAs as novel non-invasive biomarkers for early detection of gastric cancer, PLoS ONE 7 (3) (2012) (e33608).
[60] T. Kawaguchi, et al., Clinical impact of circulating miR-221 in plasma of patients with pancreatic cancer, Br. J. Cancer 108 (2) (2013) 361.
[61] F. Hong, et al., Prognostic significance of serum microRNA-221 expression in human epithelial ovarian cancer, J. Int. Med. Res. 41 (1) (2013) 64–71.
[62] C. le Sage, et al., Regulation of the p27 Kip1 tumor suppressor by miR-221 and miR-222 promotes cancer cell proliferation, EMBO J. 26 (15) (2007) 3699–3708.
[63] S. Sarkar, et al., Down-regulation of miR-221 inhibits proliferation of pancreatic cancer cells through up-regulation of PTEN, p27kip1, p57kip2, and PUMA, Am. J. Cancer Res. 3 (5) (2013) 465.
[64] J.W. Yan, J.S. Lin, X.X. He, The emerging role of miR-375 in cancer, Int. J. Cancer 135 (5) (2014) 1011–1018.
[65] X. Wu, et al., De novo sequencing of circulating miRNAs identifies novel markers predicting clinical outcome of locally advanced breast cancer, J. Transl. Med. 10 (1) (2012) 42.
[66] H. Yu, et al., Decreased circulating miR-375: a potential biomarker for patients with non-small-cell lung cancer, Gene 534 (1) (2014) 60–65.
[67] J.C. Brase, et al., Circulating miRNAs are correlated with tumor progression in prostate cancer, Int. J. Cancer 128 (3) (2011) 608–616.
[68] L. Xu, et al., The expression of microRNA-375 in plasma and tissue is matched in human colorectal cancer, BMC Cancer 14 (1) (2014) 714.
[69] L.-M. Li, et al., Serum microRNA profiles serve as novel biomarkers for HBV infection and diagnosis of HBV-positive hepatocarcinoma, Cancer Res. 70 (23) (2010) 9798–9807.
[70] K. Zhang, et al., Circulating miRNA profile in esophageal adenocarcinoma, Am. J. Cancer Res. 6 (11) (2016) 2713.
[71] W.-H. Zhang, et al., The identification of miR-375 as a potential biomarker in distal gastric adenocarcinoma, Oncol. Res. Featur. Preclin. Clin. Cancer Therap. 20 (4) (2012) 139–147.
[72] A.B. Hui, et al., Significance of dysregulated metadherin and microRNA-375 in head and neck cancer, Clin. Cancer Res. 17 (24) (2011) 7539–7550.
[73] F. Wang, et al., miR-375 is down-regulated in squamous cervical cancer and inhibits cell migration and invasion via targeting transcription factor SP1, Am. J. Pathol. 179 (5) (2011) 2580–2588.
[74] R. Morimura, et al., Novel diagnostic value of circulating miR-18a in plasma of patients with pancreatic cancer, Br. J. Cancer 105 (11) (2011) 1733.
[75] S. Jin, S.-S. Tan, H. Li, MicroRNA-18a as a promising biomarker for cancer detection: a meta-analysis, Int. J. Clin. Exp. Med. 8 (8) (2015) 12286.
[76] Y. Hou, et al., Appraising microRNA-155 as a noninvasive diagnostic biomarker for cancer detection: a meta-analysis, Medicine (2016) 95(2).
[77] J. Yan, et al., Potential Role of MicroRNA-375 as Biomarker in Human Cancers Detection: a Meta-Analysis, Biomed. Res. Int. 2017 (2017).
[78] S. Komatsu, et al., Circulating microRNAs in plasma of patients with oesophageal squamous cell carcinoma, Br. J. Cancer 105 (1) (2011) 104.
[79] T. Kawaguchi, et al., Clinical impact of circulating miR-221 in plasma of patients with pancreatic cancer, Br. J. Cancer 108 (2013) 361.
[80] T.M.K. Motawi, et al., Study of microRNAs-21/221 as potential breast cancer biomarkers in Egyptian women, Gene 590 (2) (2016) 210–219.
[81] H. Mollasalehi, R. Yazdanparast, Non-crosslinking gold nanoprobes for detection of

nucleic acid sequence-based amplification products, Anal. Biochem. 425 (2) (2012) 91–95.
[82] H. Mollasalehi, R. Yazdanparast, An improved non-crosslinking gold nanoprobe-NASBA based on 16S rRNA for rapid discriminative bio-sensing of major salmonellosis pathogens, Biosens. Bioelectron. 47 (2013) 231–236.
[83] A. Bozorgmehr, R. Yazdanparast, H. Mollasalehi, Non-crosslinking gold nanoprobe-LAMP for simple, colorimetric, and specific detection of Salmonella typhi, J. Nanopart. Res. 18 (12) (2016) 351.
[84] H. Mollasalehi, R. Yazdanparast, Development and evaluation of a novel nucleic acid sequence-based amplification method using one specific primer and one degenerate primer for simultaneous detection of Salmonella Enteritidis and Salmonella Typhimurium, Anal. Chim. Acta 770 (2013) 169–174.
[85] N. Howlader, et al., SEER Cancer Statistics Review, 1975–2012, based on November 2014 SEER data submission, posted to the SEER web site, April 2015. Bethesda, MD: National Cancer Institute; 2015, Forrás: http://seer. cancer. gov/csr/1975_2010/. (2015. június 10. 17: 41) (2014).
[86] R.-C. Zeng, et al., Down-regulation of miRNA-30a in human plasma is a novel marker for breast cancer, Med. Oncol. 30 (1) (2013) 477.
[87] R. Zheng, et al., Prognostic value of miR-106b expression in breast cancer patients, J. Surg. Res. 195 (1) (2015) 158–165.
[88] P.S. Mitchell, et al., Circulating microRNAs as stable blood-based markers for cancer detection, Proc. Natl. Acad. Sci. 105 (30) (2008) 10513–10518.