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The roles of miRNAs in human breast cancer and canine mammary tumor

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Abstract: MicroRNAs have become a hot topic in cancer research nowadays due to their important role not only on cancer development, progression, invasion but also on repression of cancer related genes. With advanced technologies, these microRNAs can easily be detected from biopsy samples and blood for early diagnosis, prognosis and treatment. Due to increasing demand of research in exploring expression profile of microRNAs with respect to different subtypes of breast cancer, this review aimed to provide an update on microRNA database available resources, canine breast cancer models, the role of microRNA as oncomir or oncosupressor, detection of microRNAs and potential of miRNAs for breast cancer treatment.

Keywords: Breast cancer, MicroRNAs, Oncomir, Oncosupressor, Targets of miRNA, Breast cancer model, miRNA profiles, miRNA database

Background

MicroRNA (miRNA) was discovered in 1993 in *Caenorhabditis elegans* [1]. These non-coding short RNAs known as miRNAs from eukaryotes such as in plants and animals are highly important for regulation of gene expression at post-transcriptional level. Further, miRNAs are also responsible for cellular growth, differentiation, proliferation and apoptosis [2]. Predominant expression of a particular miRNA varies according to the type of animal tissue. Changes of normal miRNA expression levels indicate abnormal or disease conditions of tissues or body systems. Researchers were convinced to focus more about miRNAs after they found the first miRNA lin-4 of *C. elegans* that inhibited the expression of lin-14 gene [1]. Since then researchers introduced more and more worthy new findings related to several miRNAs and their roles in different diseases and cancers including breast cancers that potentially led clinicians to be able use circulating miRNAs as affordable, non-invasive detectable biomarkers for earlier diagnosis, prognosis and treatments of breast cancers.

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Processing of microRNAs in the body

MicroRNAs (miRNAs, miRs) are 20 to 23 nucleotide RNAs and modulate gene expressions [3]. MicroRNAs processing in our body can be observed two parts as they started working in the nucleus of cells and continue its further processing in the cytoplasm [4]. The process in the nucleus initiates with the transcription of non-coding miRNAs genes with their own promoters. These primary transcriptions are carried out mainly by RNA polymerase II and the products are known as pri-miRNAs [5]. The stem-loop structure of pri-miRNAs are further processed by enzyme Drosha and dsRNA-binding protein DGCR8 [6–8]. The cleavage of pri-miRNAs produces 70 nucleotide long pre-miRNAs [9]. These pre-miRNAs are then exported into the cytoplasm by exportin 5 for further processing [10]. In the cytoplasm, pre-miRNAs are cleaved by RNase III enzyme, Dicer 1 that works together with transactivation responsive RNA binding protein 2 (TRBP) and AGO2 to generate double stranded miRNA-miRNA* duplex [11–13]. From the two miRNA strands, the guide strands or mature miRNA strands are incorporated into RISC (RNA-induced silencing complex) in order to bind its complementary target mRNA sequences of the target genes to block translation process. The passenger strands miRNA* are degraded [14, 15]. However, it was also reported that some miRNAs; e.g. miRNA 145 are processed without Dicer, alternative precursors of miRNAs called mirtrons are processed without Drosha. Some

miRNAs are processed along the pathway of tRNA [16–19]. Up to now, scientists have found miRNAs 2619 in human [20].

The process of miRNA begins in the nucleus of cells and continue in the cytoplasm of cells. Primary miRNA (pri-miRNA) transcription is done mainly by RNA polymerase II. Drosha and DGCR8 trim 100 nt to 120 nt long pri-miRNA to become a shorter 70 nt pre-miRNA and it is exported into cytoplasm by exportin 5 for further processes. Pre-miRNA in the cytoplasm is cleaved by RNase III, Dicer I and Argonaute 2 (AGO2) to become a 20 nt to 30 nt long duplex miRNA consists of a guide strand and a passenger strand. From the duplex miRNA, the strand, 3′ to 5′ miRNA known as passenger miRNA is degraded due to PIWI domain in RISC. The guide strand 5′ to 3′ miRNA which is engaged with PAZ domain in RISC binds to its target mRNAs and causes translational repression and cleavage of target mRNAs (Fig. 1).

Mechanisms of miRNA action

Single stranded mature microRNAs bind 3′ UTR (untranslated region) of target mRNAs as a post transcriptional regulation of gene expressions that inhibits translation of target mRNAs for proteins or cleavage of the target mRNAs by Argonaut ribonuclease of RISC (RNA-induced silencing complex) [21]. MicroRNA does not need to bind its whole length of complete nucleotide sequences to target mRNA but miRNA can perform gene expression regulation as long as minimum 2 to 8 base pairs are perfectly complementary between 3′ region of target mRNA and 5′ region of miRNA (miRNA seed sequence) in human and animals [22]. In human and animals, seed region of miRNA is usually 100% complementary to target mRNA but the rest sequences of miRNA may include mismatches to target mRNA that causes distended appearance due to limited base paring [23]. Two silencing mechanisms; slicer dependent that shows targeted mRNA cleavage irreversibly by Ago2 and slicer independent way that causes reversible translation repressions [24].

One miRNA can regulate concurrently the expression of many genes and thus it is involved in multiple cellular signaling pathway [3]. Furthermore, in recent studies, miRNAs was found to be involved in increasing the translation of a target mRNA directly and they were also be able to indirectly increase target mRNA levels by interacting repressor proteins which deter the translation of target mRNA [25]. MicroRNAs (miRNAs), either be as oncogenes or tumor suppressor genes play crucial role in cell differentiation, development, apoptosis and cell cycle. MicroRNAs are known to be expressed differentially in cancers but they show unique expression signature for a specific tumor type. It was reported that miRNAs influence on metastasis and resistance to different types of therapies [26]. Furthermore, researchers have found pro and anti-metastatic miRNA [27].

MicroRNAs for diagnosis, prognosis and therapeutics

Detecting circulating miRNA has also become a promising diagnostic tool. MicroRNA profiles are useful not only for diagnosis and prognosis but also for treatments in terms of choosing effective chemotherapeutic drug in cancers. This is why nowadays detecting miRNA profiles from breast cancer become more and more common in research field and also this happens to clinicians. In a study with zebra fish, researcher found that certain miRNAs dominantly expressed in specific tissues and they became noticeably reduced expression levels when the tissues are in tumors state [28]. Commonly used breast cancers diagnostic methods such as mammography, ultrasound, X-rays and MRI still exist limitations of its use in patients and also required skills to read the images for proper interpretations. Although detecting circulating miRNA is not a substitute for other conventional diagnostic methods, it simply becomes essential for most cancer diseases due to its less invasive than tissue biopsy which has to be done for genetic tests such as specific mRNA expression. It has been reported several miRNAs have been proved to be deregulated. Up-regulated miRNAs that may be used for diagnosis, prognosis and therapeutic are miR21, miR155, miR221/222, miR9, miR10b, miR29a, miR96, miR146a, miR181, miR373, miR375, miR520c and miR589 [29, 30]. Some of these up-regulated miRNAs in tumors play major role in controlling and working together with multiple targets genes and led them to be invasive types. Down-regulated miRNAs are those with tumor suppressor properties. Recent study reported that let7c is possible biomarker which can discriminate breast cancer samples grade 1 to grade 3 [3]. Other consistently down-regulated miRNAs are miR30a, miR31, miR34, miR92a, miR93, miR125, miR126, miR146a, miR195, miR200, miR205, miR206, miR503 and let7 family.

In breast cancer stem cells, miR15/16, miR103/107, miR128b, miR145, miR200 and miR335 are found to be down-regulated. With great efforts, now total 130 over miRNAs signatures were identified to distinguish between normal and tumor breast tissue accurately [31]. MicroRNAs in breast cancers can be classified into Oncomirs, Oncosupressors and MetastamiRs [32]. Oncomirs disturb expression of oncosupressors and cells apoptosis. In human breast cancer, oncomirs miRNA21 and miRNA155 are outstandingly upregulated and oncosupressors miRNA10b, miRNA125b and miRNA145 are noticeably downregulated. In triple negative breast cancers, miRNA21, miRNA 210 and miRNA 221 were

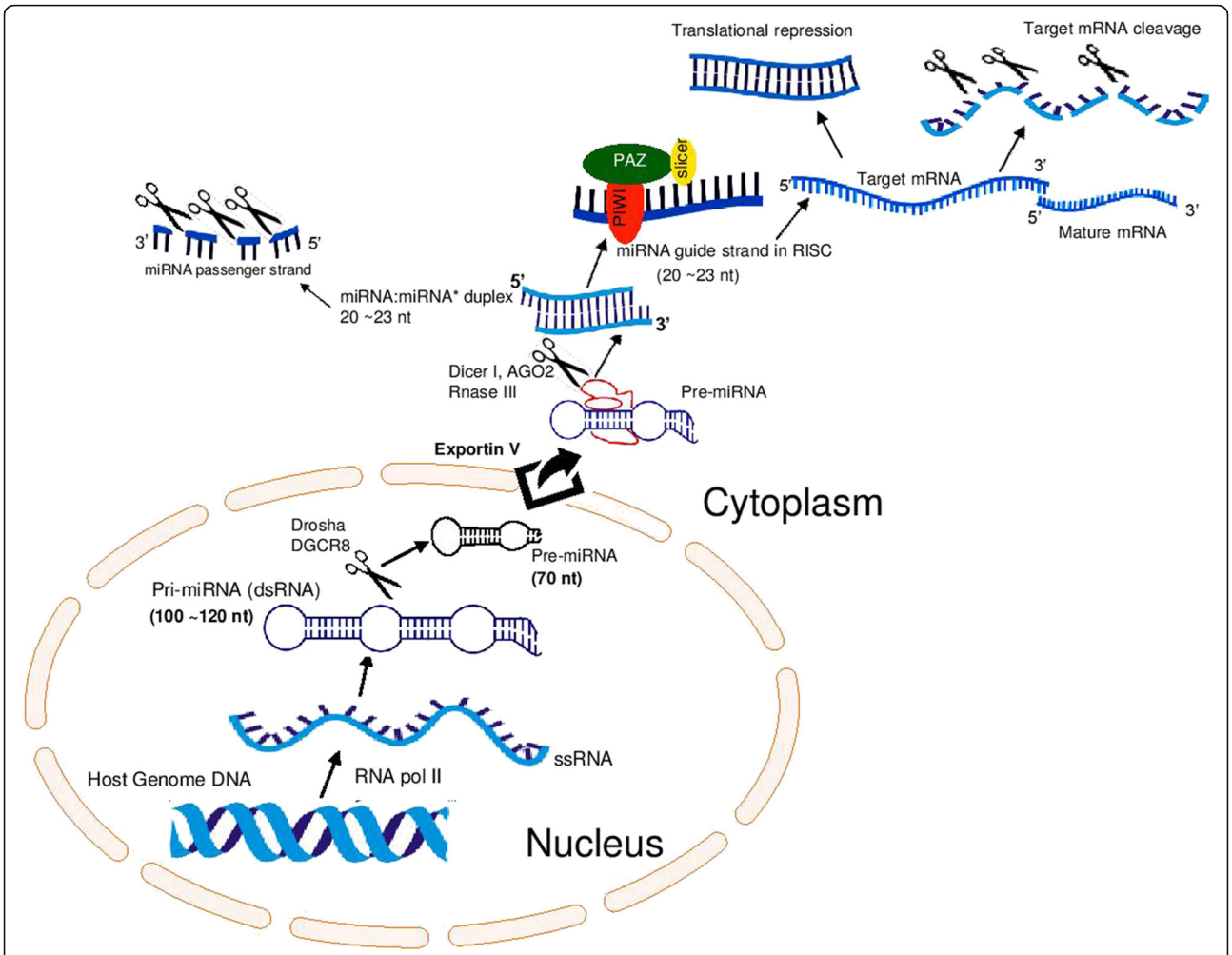

Fig. 1 MicroRNA Processing Steps Pathways. The process begins in the nucleus of cells and continue in the cytoplasm of cells. Primary miRNA (pri-miRNA) transcription is done mainly by RNA polymerase II. Drosha and DGCR8 trim 100 nt to 120 nt long pri-miRNA to become a shorter 70 nt pre-miRNA and it is exported into cytoplasm by exportin 5 for further processes. Pre-miRNA in the cytoplasm is cleaved by RNase III, Dicer I and Argonaute 2 (AGO2) to become a 20 nt to 30 nt long duplex miRNA consists of a guide strand and a passenger strand. From the duplex miRNA, the strand, 3′ to 5′ miRNA known as passenger miRNA is degraded due to PIWI domain in RISC. The guide strand 5′ to 3′ miRNA which is engaged with PAZ domain in RISC binds to its target mRNAs and causes translational repression and cleavage of target mRNAs

found to be upregulated. Anti-miRNAs to those upregulated oncomirs not only inhibited cancer cells growth but also increased apoptosis and decreased cell proliferation. Oncosupressors such as miR204, miR34a,b,c and let-7 family of microRNAs are found to be down-regulated in breast cancers. In one study, let-7 mimics showed effectiveness in the treatment of lungs cancer in mouse model when it was administered I.V. in the form of neutral lipid emulsion. MetastamiRs are recently recognized and introduced to those small non-coding miRNAs that regulates migration and invasion of cancer cells [33, 34]. These metastamiRs plays as major role in epithelial-mesenchymal transition (EMT), apoptosis and angiogenesis. It was reported that miRNAs 10b expression is 50% higher in invasive type of cancer cell line MDA-MB-231 compare to non-invasive type MCF-7 cancer cell line. Although miRNA10b was found to be down-regulated in non-invasive breast cancers, its change to up-regulation indicates the initiation of breast cancer metastasis. A study shown that applying antisense miR10b inhibitor oligonucleotides reduces invasiveness of transfected cells. It is required to restore the level of miRNAs to normal state and this can be achieved by dosing miRNA mimics or inhibitors, introducing miRNA genes with a DNA vector, application of small molecules to reverse epigenetic silencing of miRNAs [28]. MicroRNAs mimics are short double stranded RNA guide strand and passenger stand oligonucleotides. They may be fully or partially complementary each other. The list of down-regulated miRNAs has been published and each of them are indeed potential cancer therapeutic miRNAs. It was also known that one therapeutic miRNA is

able to target multiple mRNAs. In vivo study further provided an evidence that silencing of overexpression miR10b with systemic antagomirs suppressed breast cancer metastasis in mice [35]. Another study reported that miR373 was up-regulated in patients with breast cancer metastasized to lymph nodes. Like other circulating miRNAs, metastamiRs also become a popular molecular marker for breast cancers. Circulating miRNAs biomarkers offered affordable and non-invasive method of early detection, differentiating subtypes of breast cancers which allows clinicians to predict prognosis and further adjust their treatment regime as required. Table 1 miRNAs expression level, their targets, functional roles and potentials as biomarker in human breast cancer (female).

Methods to detect miRNAs in breast cancer

Micro-RNAs are quite a smaller size and impossible to detect them with the methods used for mRNA. However, since miRNAs roles become important and also found to be significant biomarkers of diseases including cancers, scientists invested enormous efforts in order to detect them. Nowadays, about 30 methods in total are available to detect miRNA expression profiles. MicroRNA expression profiles in certain diseases, give critical useful information about diagnosis and prognosis. Among these miRNA detection methods, commonly applied to detect miRNA are Northern blotting, Microarray, Bead based flow cytometry, qRT-PCR, In sithu hybridization and Next-Generation Sequencing [36]. Among them, the most standardized method for miRNA analysis is Northern blotting although it is low-throughput [37].

Being a high throughput, miRNA microarrays can be applied several miRNAs in a large number of samples. However, miRNA microarrays is low specificity and low sensitivity due to their extremely short sequence which allows only very little room to fine-tune the hybridization conditions of miRNAs [38]. Another high throughput, high specificity and high sensitivity method for assessment of miRNA is qRT-PCR and this method can also be used for validation of data obtained from other detection platforms [39]. Bead-based flow cytometry and in situ hybridization detection methods are limited to known miRNA structures. However, the latest detection method which gives high throughput, high specificity and high sensitivity is Next-generation sequencing and this method allows to discovery of new miRNA as well as to confirm known miRNA [40].

In breast cancers, miR10b, miR125b and miR145 are consistently found to be down-regulated and miR21, miR155 are consistently up-regulated [41, 42]. It was also reported that miRNAs can still be detected from formalin fixed and paraffin embedded tissue samples, collected blood and serum too. MicroRNAs are stable due to their smaller size that showed tolerance to ribonuclease degradation.

Breast cancer model

All previous studies have identified that canine mammary tumor models are great to study the molecular pathogenesis of human breast cancer due to several similarities such as epidemiological factors and histopathological aspects [43–46]. In addition, it is very common that dogs and humans are exposed to equivalent carcinogens as frequently they are living in the same environment. Risk factors and molecular changes in affected mammary tissues for both species are comparable. Most of canine mammary tumors and human breast cancers are also originated from epithelial tissues [47]. In fact, different types of human cancers can be found in dogs too. For example, lymphoma, breast cancer, bone cancer and etc. Furthermore, studies have pointed out specifically that the age of onset and peak incidence among humans and dogs are about the same if their age is calculated proportionately [43]. Spontaneous mammary tumors incidence rate in female dogs is about 25% (1 in 4) while breast cancer incidence rate in women is about 12% (1 in 8). Readily availability of spontaneous canine mammary tumors is one of the factors that makes them a good model to study breast cancer as an alternative to experimental animal models. In particular, similarities including expression of hormone receptors, tumor growth markers, epidermal growth factor receptor, and P53 mutations also strengthen the canine mammary tumor model. Moreover, overexpression of cyclooxygenase-2 (COX-2), a molecule directly involved with mammary carcinogenesis, and matrix metalloproteinase-2 (MMP-2) which plays a role in invasion and metastasis process was detected in both species too [48, 49].

It is noted that miRNA genes between human and canine are highly conserved. A study had been reported that miR15a, miR16, miR17-5p, miR21, miR29b, miR125b, miR155, miR181b and let7 family expression patterns were the same between human breast cancer and canine mammary tumors except miR145 which does not showed changes in canine [50, 51]. As in human breast cancer, miR15a and miR16 expressions were also reduced in canine mammary carcinomas. Furthermore, miR15a and miR16 were shown to be involved in differentiation of malignancy [51]. Computationally analysis results showed that 300 miRNAs amongst canine miRNAs were found to have the same sequences as of those found in human [52]. Also, it has been described that miRNA210 which is regulated by hypoxia, was significantly upregulated in continuous manner throughout canine mammary tumor progression [53]. In human breast

Table 1 miRNAs expression level, their targets, functional roles and potentials as biomarker in human breast cancer (female)

miRNA Human (Female)	Sample Source	Expression Level	Target	Functional Role, Biomarker as Diagnostic, Prognostic, Therapeutic	Authors, year of publication
Let 7 family	Cell line, Tissue, Blood, Serum	Down	RAS, HMGA2, H-RAS, KRAS, MYC, CCND2, PBX3, LIN28, PEBP1, BMI-1	Proliferation, differentiation, self-renewal, EMT, Tamoxifen response, diagnostic and prognostic biomarker	Kurozumi et al. 2016 [57], Bertoli et al. 2015 [3] Schooneveld et al. 2015 [36], Kaboli et al. 2015 [58], Takahashi et al. 2015 [59], Zhang et al. 2014 [60], Schwarzenbacher et al. 2013 [61], Fu et al. 2011 [62], O′ Day et al. 2010 [2]
7	Tissue	Down	FAK, IGFR, EGFR, REGγ	Regulating gene expression, cell growth and survival control, Tamoxifen response, Docetaxel and Cisplatin sensitive, diagnostic biomarker	Bertoli et al., 2015 [3], Kaboli et al. 2015 [58]
9	ER+ tissue, Cell line	Up	CCND1, E-CAD, CDH1	Regulate CDKs and control cell cycle progression G1 to S, cellular adhesion and metastasis, diagnostic and prognostic biomarker	Bertoli et al., 2015 [3], Kaboli et al. 2015 [58], Schooneveld et al. 2015 [36], Zhang et al. 2014 [60]
10b	Cell line, Tissue	Up	HOXD 10, SYNDECAN-1, TIAM1, E-CAD, RHOC	Promote cell migration, invasion, metastasis, EMT, stemness of BCSC, Tamoxifen resistance, diagnostic biomarker	Bertoli et al. 2015 [3], Schooneveld et al. 2015 [36] Kaboli et al. 2015 [58], Takahashi et al. 2015 [59], Shafi et al. 2014 [32], Zhang et al. 2014 [60], Fu et al. 2011 [62], O′ Day et al. 2010 [2]
16	Plasma, Tissue, Cell line, Serum	Down	WIP1, BCL2, E2F, CDK6, CCND1	Regulate cell proliferation and death, diagnostic and prognostic, Doxorubicin and Docetaxel response	Bertoli et al. 2015 [3], Kaboli et al. 2015 [58], Zhang et al. 2014 [60], Schwarzenbacher et al. 2013 [61],
17-5p	Tissue	Down	E2F1, CCND1, AIB1	Regulate CDKs and control cell cycle progression G1 to S, cancer cell proliferation, diagnostic biomarker	Kurozumi et al. 2016 [57], Bertoli et al. 2015 [3], Fu et al. 2011 [62], O′ Day et al. 2010 [2]
17/92	Cell line	Up	E2Fs, ER*α*, C-MYC, AIB1, CYCLIN D1, MEKK2	Control cell cycle, proliferation, tumorigenesis, proapoptosis, metastasis	Kaboli et al. 2015 [58], Schooneveld et al. 2015 [36], Xiang et al. 2010 [63], Bonauer et al. 2009 [64]
21	Plasma/Tissue/ Cell line, Serum, Blood	Up	PTEN, BCL-2, TPM1, TIMP3, HER, PDCD4, MASPIN, CDC25, PTEN, BCL2, RHOB, MMPs, HIF1A	Promote cell migration, invasion, metastasis, EMT, diagnostic and prognostic biomarkers, resistant to Cisplatin, Doxorubicin, Topotecan	Kurozumi et al. 2016 [57], Bertoli et al. 2015 [3], Schoonevel et al. 2015 [36], Kodahl et al.2014 [65], Shafi et al. 2014 [32], Zhang et al. 2014 [60]
22	Cell line	Down	CDK6. SIRT1, SP1, TET1–3, TIP60	Regulator of cellular senescence, inhibit tumor growth and metastasis, regulate EMT genes by repressing TIP60, prognostic biomarker (TIP60/miR-22)	Kaboli et al. 2015 [58], Takahashi et al. 2015 [59], Schwarzenbacher et al. 2013 [61]
27a	Tissue	Up	FOXO1, ZBTB10/RINZF, MYT-1, ZBTB10	Cell cycle progression G2 to M check point regulation, tumor development, invasion and metastasis, diagnostic and prognostic biomarker	Kurozumi et al. 2016 [57], Bertoli et al. 2015 [3], Zhang et al. 2014 [60], Tang et al. 2012 [66], Fu et al. 2011 [62], Mertens-Talcott et al. 2007 [67]
27b	TNBC, Cell line and tissue	Up	CYP1B1, ARFGEF1, FOXO1, PPARγ, ST14, NISCH	Regulate cell cycle progression, proliferation, metastasis, angiogenesis, drug resistance, generation of breast cancer stem cells (BCSCs), prognostic biomarker	Ding et al. 2017 [68], Kurozumi et al. 2016 [57], Bertoli et al. 2015 [3], Zhang et al. 2014 [60], Schoonevel et al. 2015 [36], Fu et al. 2011 [62]
29b	Tissue	Down	ITGB1, MMP2, TIAM1, VEGFA, ANGPTL4, LOX	Inhibit proliferation, angiogenesis and metastasis. Diagnostic biomarker	Kurozumi et al. 2016 [57], Bertoli et al. 2015 [3]
30	TNBC, Cell line and BCSCs	Down	UBC9, ITGB3, AVEN	Regulate self-renewal and antiapoptotic, in-vitro mammosphere formation.	Bertoli et al. 2015 [3], Kaboli et al. 2015 [58] Schwarzenbacher et al. 2013 [61]
30c	Tissue	Down	TWF1, IL-11, VIM	Tamoxifen response, suppresses interleukin 11 expression and inhibit resistance to paclitaxel and doxorubicin	Kurozumi et al. 2016 [57], Bertoli et al. 2015 [3], Takahashi et al. 2015 [59]

Table 1 miRNAs expression level, their targets, functional roles and potentials as biomarker in human breast cancer (female) *(Continued)*

31	BC and TNBC cell line	Down	RHOA, RDX, ITGA5, FZD3, M-RIP, MMP16, WAVE3, PKCepilon	Inhibits several steps of the invasion-metastasis cascade in breast cancer	Kurozumi et al. 2016 [57], Bertoli et al. 2015 [3], Kaboli et al. 2015 [58], Schooneveld et al. 2015 [36], Zhang et al. 2014 [60], Fu et al. 2011 [62], O′ Day et al. 2010 [2]
34a, b, c	BC and TNBC cell line, Tissue	Down	NOTCH4, NOTCH 1, CCND1, AXL, WIP1 C-MYC, FRA1, CDK4, CDK6, SIRT1, E2F3	Cell Cycle control, invasion and metastasis, EMT, self-renewal and EMT, diagnostic biomarker, radiotherapy sensitive	Bertoli et al. 2015 [3], Zhang et al. 2014 [60], Schwarzenbacher et al. 2013 [61] Kaboli et al. 2015 [58], Fu et al. 2011 [62] O′ Day et al. 2010 [2]
125a-5p	Cell line, Tissue	Down	HDAC4, HDAC5, HER3, HUR	Inhibit cell proliferation and differentiation, induce apoptosis, Docetaxel sensitive, diagnostic biomarker	Hsieh et al. 2015 [69], Bertoli et al. 2015 [3], Kaboli et al. 2015 [58], Zhang et al. 2014 [60]
125b	Cell line, Tissue	Down	HER2, EST1, E2F3, EPO, EPOR, ENPEP, CK2-α, CCNJ, MEGF9, ERBB2, HUR, BAK	Inhibit cell proliferation and differentiation, diagnostic biomarker, FEC chemotherapy resistant, Taxol resistant, Trastuzumab sensitive.	Kurozumi et al. 2016 [57], Bertoli et al., 2015 [3], Schooneveld et al. 2015 [36], Zhang et al. 2014 [60], Feliciano et al. 2013 [70], Wang et al. 2012 [71]
126	BC and TNBC cell line, Tissue	Down	IGFBP2, PITPNC1, MERTK, VEGF, IRS-1, PIK3R2	Cell cycle progression from G1/G0 to S, reduces metastasis and angiogenesis, diagnostic biomarker	Kurozumi et al. 2016 [57], Bertoli et al. 2015 [3], Zhang et al.2014 [60], Fu et al. 2011 [62]
128	Cell line and BCSCs	Down	BMI-1, ABCC5	Regulate cell cycle, inhibit tumor growth and angiogenesis, Doxorubicin sensitive	Bertoli et al. 2015 [3], Kaboli et al. 2015 [58], Schwarzenbacher et al. 2013 [61]
143	Serum	Down	HER3	Inhibit cell invasion and metastasis, diagnostic biomarker	Schooneveld et al. 2015 [36], Kaboli et al. 2015 [58], Kodahl et al. 2014 [65]
145	Serum/ Plasma/Tissue, Cell line	Down	EGF, C-MYC, VEGF, N-CADHERIN, HIF-2α, MUCIN1, HER3, IRS1, RTKN	Inhibit cell invasion and metastasis, diagnostic biomarker	Bertoli et al. 2015 [3], Schooneveld et al. 2015 [36], Zhang et al. 2014 [60], Kodahl et al. 2014 [65] Fu et al. 2011 [62]
146	BC and TNBC cell line, Tissue	Down	BRCA1, NFκB, TRAF6, IRAK1, ROCK1, CXCR4, EGFR	Proliferation, antiapoptotic, diagnostic biomarker	Bertoli et al. 2015 [3], Shafi et al. 2014 [32]
146a	BC and TNBC cell line, Tissue	Down	ICAM1, VHRF1, NF-Kb, EGFR	Antimetastasis, symmetric and asymmetric division of CSCs	Kurozumi et al. 2016 [57], Bertoli et al. 2015 [3], Kaboli et al. 2015 [58]
146b	BC and TNBC cell line, Tissue	Down	ICAM1, VHRF1, NF-κB, STAT3, EGFR	Anti-metastasis	Kurozumi et al. 2016 [57], Schooneveld et al. 2015 [36], Kaboli et al. 2015 [58]
155	Serum, Heterogenous BC, Tissue	Up	CXCR4, FOXO3, TRF1, SHIP, TP53INPI, RHOA, SOCS1	Cell growth, proliferation, metastasis, telomere synthesis, TGF- β Signaling, diagnostic and prognostic biomarker, Taxane response	Bertoli et al. 2015 [3], Schooneveld et al. 2015 [36], Kodahl et al.2014 [65], Zhang et al. 2014 [60], Kaboli et al. 2015 [58], Fu et al. 2011 [62], O′ Day et al. 2010 [2]
181	Cell line and BCSCs, Serum	Up	ATM	Regulate in vitro mammosphere formation, anti-apoptotic	Bertoli et al. 2015 [3], Schwarzenbacher et al. 2013 [61], Kaboli et al. 2015 [58]
181b	Tissue, Blood, Cell line	Up	SMAD3, BIM, CDK8	Promotes cell proliferation, migration and metastasis, associated with the resistance to Doxorubicin, diagnostic biomarker	Zheng et al. 2015 [72], Kaboli et al. 2015 [58]
182	Cell line and tissue	Up	BRCA1, FOXO1	Proliferation, antiapoptotic, Tamoxifen response	Kurozumi et al. 2016 [57], Bertoli et al. 2015 [3] Kaboli et al. 2015 [58], Zhang et al. 2014 [60]
194	Tissue	Up	TLN2, CDH2, RAC1, THBS1, ITGA9	Antimetastastic, inhibit cell migration, enhance chemosensitivity, associate with trastuzumab (Herceptin) response, diagnostic biomarker.	Bertoli et al., 2015 [3], Kaboli et al. 2015 [58], Calura et al. 2014 [73], Le et al. 2012 [74]
199b-5p		Down	HER2		Fang et al. 2016 & 2013 [75, 76]

Table 1 miRNAs expression level, their targets, functional roles and potentials as biomarker in human breast cancer (female) *(Continued)*

	Tissue, Cell line			Regulate proliferation, invasion and metastasis, prognostic biomarker	
200	Tissue and Cell line	Down	BMI-1, SUZ12, ZEB1, ZEB2, PLCG1, TGFβ2, FAP-1, SNAI-1, SNAI-2, CTNNB1	Reduces tumor growth, anti-metastatic, stemness and EMT.	Bertoli et al. 2015 [3], Kaboli et al. 2015 [58], Shafi et al. 2014 [32], Hilmarsdottir et al. 2014 [77], Schwarzenbacher et al. 2013 [61], O′ Day et al. 2010 [2]
200a	Tissue and Cell line	Down	SLUG, BMI1, ZEB1, ZEB2, EPHA2	Reduces tumor growth, anti-metastatic	Tsouko et al. 2015 [78], Bertoli et al. 2015 [3], Kaboli et al. 2015 [58]
200b	Tissue and Cell line	Down	SP1, RAB21, RAB23, RAB18, RAB3B	Control cell proliferation and apoptosis, Prognostic biomarker	Yao et al. 2015 [79], Ye et al. 2014 [80]
200c	Tissue and cell line	Down	BMI1, ZEB1, ZEB2, FHOD1, PPM1F	Reduces tumor growth, antimetastatic, inhibit clonogenicity of BCSCs, induce differentiation, sensitize breast cancer cells to doxorubicin, therapeutic biomarker	Bertoli et al. 2015 [3], Kaboli et al. 2015 [58], Zhang et al. 2014 [60], Jurmeister et al. 2012 [81], Fu et al. 2011 [62], Shimono et al. 2009 [82]
204	Tissue and cell line	Down	JAK2, ZEB2, FOXA1, BDNF, IL-11, PDEF, SIX1, SAM68	Inhibit cell growth, invasion and metastasis, induce cell apoptosis, suppress BCSCs, diagnostic and prognostic biomarker, Tamoxifen response	Shen et al. 2017 [83], Li et al. 2016 [84], Flores-Pérez et al. 2016 [85], Bertoli et al. 2015 [3]
205	Ductal BC,BC and TNBC cell line	Down	HER3, E2F, P53, ZEB-1, HMGB3, VEGF-A, BRBB3	Inhibit proliferation, invasion and EMT, prognostic biomarker	Bertoli et al. 2015 [3], Schooneveld et al. 2015 [36], Takahashi et al. 2015 [59], Zhang et al.2014 [60], Fu et al. 2011 [62]
206	BC and TNBC cell line	Down	ERα, CCND2, ESR1, NOTCH3, SRC-1, SRC-3, GATA-3, ERα, Cx43	Reduces migration, invasion and anti-metastatic	Bertoli et al. 2015 [3], Schooneveld et al. 2015 [36], Kaboli et al. 2015 [58], Shafi et al. 2014 [32], Zhang et al. 2014 [60], Fu et al. 2011 [62], O′ Day et al. 2010 [2]
210	IDC, Cell line, Tissue, Plasma	Up	E2F3, NPTX1, RAD52, ACVR1B, MNT, CASP8AP2, FGFRL1, HOXA-1, HOXA-9	Prognostic and diagnostic biomarker, Herceptin resistance	Bertoli et al. 2015 [3], Schooneveld et al. 2015 [36], Devlin et al. 2011 [86], Huang et al. 2010 [87]
216b	Tissue and cell line	Down	SDCBP, P2X7	Suppress breast cancer growth and metastasis, proapoptoic, therapeutic biomarker	Jana et al. 2016 [88], Kaboli et al. 2015 [58], Zheng et al. 2014 [60]
222	Serum, Tissue	Up	ABCG2, MMP1, SOD2, TIMP3, GNAI3	Inhibit migration and invasion, enhance breast cancer cells to cisplatin responsiveness, diagnostic and prognostic biomarker	Bertoli et al. 2015 [3], Schooneveld et al. 2015 [36], Zhao et al. 2015 [89], Kodahl et al. 2014 [65]
221/222	Cell line	Up	ERα, P27kip1, KIT, P57, PTEN	Tamoxifen resistant luminal type breast cancer and Fulvestrant resistant	Bertoli et al. 2015 [3], Takahashi et al. 2015 [59] Piva et al. 2013 [30], Fu et al. 2011 [62]
224	Tissue and Cell line	Up	CXCR4, CDC42, RKIP, FZD5, FZD4,	Inhibited cell proliferation and migration	Liu et al. 2014 [90], Zhang et al.2014 [60]
335	Cell line, Tissue	Down	SOX4, SPL, BCL-W, SOX4, TNC, PTPRN2, MERTK, RSP1, IGF1, ID4, ERα	Suppress metastasis and migration, proapoptotic, diagnostic and prognostic biomarkers	Bertoli et al. 2015 [3], Schooneveld et al. 2015 [36] Kaboli et al. 2015 [58], Shafi et al. 2014 [32], Zhang et al. 2014 [60]
339-5p	Tissue	Down	BCL6	Proapoptotic, Tamoxifen response	Bertoli et al. 2015 [3], Kaboli et al. 2015 [58]
342-5p	Heterogenous BC, Tissue	Down	EGRF, HER2, AKT, PKC, ESR1, ERN2, PELP1, SRC	Regulate cell cycle, antiproliferative, diagnostic and prognostic biomarker, regulate Tamoxifen response	Bertoli et al. 2015 [3], Schooneveld et al. 2015 [36] Kaboli et al. 2015 [58], Leivonen et al. 2014 [91], Romero-Cordoba et al. 2012 [92]
373	Cell line	Up	CD44	Cell migration, invasion and metastasis	

Table 1 miRNAs expression level, their targets, functional roles and potentials as biomarker in human breast cancer (female) *(Continued)*

					Bertoli et al. 2015 [3], Schooneveld et al. 2015 [36], Shafi et al. 2014 [32], Fu et al. 2011 [62]
429	Cell line, Tissue	Down	ZEB1, ZEB2, CRKL, TUBB2A, TGF-β, XIAP	Anti-proliferative and anti-metastatic, member of miR-200 family	Takahashi et al. 2015 [59], Ye et al. 2015 [93], Kaboli et al. 2015 [58], Wang et al. 2015 [94]
491-5p	Cell line, Tissue	Down	EGRF, HER2, NNAT, JMJD2B	Antiproliferative, antimetastatic especially estrogen stimulated breast cancer cells	Hui et al. 2015 [95], Kaboli et al. 2015 [58]
495	Cell line, BCSCs	Up	REDDI, ECAD	Increased tumor formation, downregulation of E-cadherin, maintaining a stem-cell line phenotype	Kaboli et al. 2015 [58], Schwarzenbacher et al. 2013 [61]
520c	Cell line, Tissue	Up	CD44	Cell migration, invasion and metastasis, Tamoxifen response	Bertoli et al. 2015 [3], Kaboli et al. 2015 [58]
708	Tissue, Cell line	Down	NNAT	Anti-proliferative and anti-metastatic	Kurozumi et al. 2016 [57], Kaboli et al. 2015 [58], Ryu et al. 2013 [96]

cancer, upregulated miRNA210 was reported as a diagnostic and prognostic marker [3, 36].

A study reported that protein expression profiles were comparable between canine mammary tumors and human breast cancers. However, 12 other differentially expressed proteins in metastatic canine mammary tumors have not been studied yet and it remains to be established whether they are associated or not with metastasis of human breast cancers [54]. It is noted that researchers are able to study myoepithelial cell proliferation in canine breast cancer model rather than in human breast cancer due to their incidence rate > 20% and <0.1% respectively [55].

Besides the aforementioned similarities between canine and human breast cancers, other aspects that make canine tumors a good model for human breast cancer is faster aging (7 times more) compared to human due to their shorter life span and additionally the average shorter overall survival rate of dogs diagnosed with cancers [56].

Resources of miRNAs database

MicroRNA database including targets of miRNAs can be retrieved from the following web-based online programs.

1. miRBase: http://www.mirbase.org/

This site was founded by Sam Griffths-Jones and currently governed by Griffiths-Jones lab of University of Manchester, UK. The version 1 of miRNAs database was introduced in 2002 with 218 entries. Total entries became 28, 645 in their latest version 21 that was released in 2014. These entries can be viewed and downloaded by names, keywords, references and annotations of respective miRNAs. This site is also available for naming of newly found miRNAs in order to avoid overlaps.

2. miRwalk: http://zmf.umm.uni-heidelberg.de/apps/zmf/mirwalk2/

Current version is miRNA walk2 and the site handle 15 different species' information on genes, mRNA and miRNA. This website is controlled by University Heidelberg, Faculty of medicine, Germany. Total 11,748 miRNA and 308,700 genes are documents in this version and generate predicted and validated miRNA-target interactions.

3. miRTarBase: http://mirtarbase.mbc.nctu.edu.tw/

This site was established by Department of Biological Science and Technology, institute of Bioiformatics National Chiao Tung University of Taiwan. This site is mainly used for identifying not only miRNA targets but also to understand interaction networks such as biological functions of miRNAs against their targets in biological pathways (KEGG pathways).

4. miRNAmap: http://mirnamap.mbc.nctu.edu.tw/

Established from the same organization mentioned above in (3). This site facilitates to search experimental verified microRNAs as well as experimental verified miRNA target genes in human, mouse, rat, and other metazoan genomes. Data recorded in this site includes expression profiles of 224 human miRNAs in 18 major normal tissues.

5. miRGator: http://mirgator.kobic.re.kr/

miRGator is based in Seoul, Korea. Current version 3 provides deep sequencing data of miRNAs that facilitate users to comprehend precursor of miRNAs, its sequences, their final products. Furthermore, miRGator has another two features such as miRNA catalogues and Expression profiles, and miRNA-mRNA target relations and expression correlations.

6. miRDB: http://mirdb.org/miRDB/

This data based was created by the department of radiation oncology, Washington university school of medicine in St. Louis. This web page provides predicted microRNA targets in human, mouse, rat, dog and chicken. This miRDB search engine allows users to search targets of miRNAs by miRNA name directly or gene accession number from GenBank, Gene Symbol and NCBI Gene ID.

7. PhenomiR: http://mips.helmholtz-muenchen.de/phenomir/

Established by German Research Center for Environmental Health. Differentially regulated miRNA expression in diseases and other biological processes can be divulged from this site.

8. miRecords: http://c1.accurascience.com/miRecords/

The Predicted Targets component of miRecords generates integrated results from 11 established miRNA target prediction programs such as DIANA-microT, MicroInspector, miRanda, MirTarget2, miTarget, NBmiRTar, PicTar, PITA, RNA22, RNAhybrid, and TargetScan/TargertScanS.

9. miRGen: http://carolina.imis.athena-innovation.gr/diana_tools/web/

miRGen, developed at the University of Pennsylvania, generates miRNA gene transcription start sites (TSSs), coupled with genome wide maps of transcription factor (TF) binding sites in order to understand mechanisms of miRNA transcription regulation.

Other useful online miRNA related sites were microrna.org, targetscan.org, ChIPBase, TarBase, starBase, ebi.ac.uk, PmmR (Putative microRNA-microRNA Regulations) and pictar.mdc-berlin.de.

Conclusion

MicroRNAs can be easily detected with advanced technologies and the continuous investigations supply miRNA as a novel clue for diagnosis and prognosis marker to therapeutic targets. Furthermore, research on delivering miRNAs mimics and/or inhibitors directly into breast cancer tissue to regulate the balance of miRNAs is gaining attention in the field. The miRNA resources mentioned in this paper are useful to generate predicted targeted mRNAs for interested miRNAs candidate. Aberrant miRNA expression in our body such as oncomirs (upregulated miRNAs) and oncosupressors (downregulated miRNAs) could be the sign of diseases and they can be clinically detected by RT-qPCR, digital PCR, microarrays, and next generation sequencing technologies. Signature miRNA profile can be used to distinguish the stages of breast cancer progression and help in early diagnosis, prognosis, and effective treatment for human breast cancer and canine mammary tumor.

Abbreviations

AGRO2: Protein argonaute-2; DGCR8: Digeorge syndrome chromosomal region 8; KEGG: Kyoto encyclopedia genes and genomes; miR/miRNA: microRNA; MRI: Magnetic resonance imaging; mRNA: messenger RNA; PAZ: Protein PAZ; PIWI: Protein PIWI; pre-miRNA: precursor microRNA; pri-miRNA: primary microRNA; RISC: RNA-induced silencing complex; TRBP: TAR RNA binding protein; tRNA: transfer RNA

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Authors' contributions

RMCY wrote and reviewed the manuscripts. CYK constructed and reviewed the manuscript. Both authors read and approved the final manuscript.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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