Role of let-7 family microRNA in breast cancer

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ABSTRACT
Metastasis and resistance to therapy significantly contribute to cancer-related deaths. Growing body of evidence suggest that altered expression of microRNAs (miRNAs) is one of the root cause of adverse clinical outcome. miRNAs such as let-7 are the new fine tuners of signaling cascade and cellular processes which regulates the genes in post-transcriptional manner. In this review, we described the regulation of let-7 expression and the involvement of molecular factors in this process. We discussed the mechanism by which let-7 alter the expression of genes involved in the process of tumorigenesis. Further, we listed the pathways targeted by let-7 to reduce the burden of the tumor. In addition, we described the role of let-7 in breast cancer metastasis and stemness properties. This article will provide the in-depth insight into the biology of let-7 miRNA and its role in the breast cancer progression.

1. Introduction
Breast cancer (BC) is most frequently diagnosed cancer and remains the leading cause of cancer-related death in women worldwide [1,2]. Altered signaling pathways [3–7], mutation in genes [8], activation of oncogenic pathways [9–11], DNA damage [12,13] and non-targeted effects of chemotherapeutic agents [14–17] significantly contributes in cancer progression. Therapeutic strategies including chemotherapy [18], application of toxins obtained from pathogens [19–24] have shown limited clinical efficacy against cancer. During past one and half decade, enormous growth in the field of microRNAs (miRNAs) biology have been witnessed and it has been suggested that targeting these small molecules holds potential therapeutic efficacy for cancer [25–27]. miRNAs are evolutionary conserved, single-stranded and contains approximately 22 nucleotides RNA molecules that alter the expression of gene at the post-transcriptional level [28]. In nucleus miRNAs are transcribed by RNA polymerase II as pri-miRNAs and subsequently cleaved by ribonuclease III, Drosha, to form a ~70 nucleotide long pre-miRNA. Thereafter, the pre-miRNA are transported to the cytoplasm and processed by the RNase III protein, Dicer, to yield 18–25 nucleotide long miRNA duplex. After unwinding, one of the strands incorporated into the RNA-induced silencing complex, that subsequently interacts with complementary sequences in the 3’ untranslated regions (3’ UTRs) of the target mRNA transcripts. A single miRNA is capable of regulating multiple miRNAs of various functions. Further, dysregulation of miRNAs abrogate the normal functioning of the cellular system that promotes several pathological conditions such as cancer [29,30].

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progression.

2. Regulation of miRNA let-7 expression

Role of let-7 in cell proliferation and differentiation have been demonstrated in animal and human cell lines [36–38]. Interestingly let-7 has been implicated in inhibiting the growth of cancer cells [39,40], microRNA let-7 expression is important to explore as it involved in the tumor suppression. let-7 expression is controlled at various stages biogenesis which involves numerous factors and signaling molecule (Fig. 1). In this section we described the factors that are known to regulate the expression of let-7 in BC.

2.1. Regulation of miRNA let-7 by Lin28

Lin28 encodes a RNA-binding protein that is known to bind let-7 pre-microRNA. The activity of let-7 was demonstrated to be affected by mutations in Lin28 [30]. Lin28 and its subtype Lin28B have been suggested to bind to hairpin and the stem of pri-let-7 and inhibit the processing of Dicer, thus inhibiting its processing and biogenesis [41,42]. In addition, binding of Lin28 to the terminal loop region of let-7g has also been demonstrated [43]. Importantly, the zinc-finger and cold-shock domains in Lin28 were determined to be crucial for pre-let-7 binding. Further, upregulation of Lin28 were shown to inhibit the let-7g processing. Ectopic expression of Lin28 abrogates the processing of pri-let-7a suggesting, that Lin28 is important to block the microprocessor-mediated cleavage of pri-let-7 miRNAs [44]. Further, the transfection of Lin28 reduces the endogenous levels of let-7 [44]. Other than Drosha/Dicer inhibition, Lin28/ Lin28B is shown to block the let-7 processing by terminal uridylation of pre-let-7 that leads to the irreversibly re-routing pre-let-7 to a degradation pathway [45]. Several enzymes including Zcchc11, a terminal uridylyl transferase 4 (TUT4) have been suggested to be involved in the progress of terminal uridylation. The TUT4 has been found to promote the pre-let-7 uridylation and blockade of let-7 processing in mouse embryonic stem cells [46]. Lin28 recruit TUT4 to pre-let-7 by recognizing tetrancleotide sequence motif (GGAG) in the loop. Later the TUT4 adds an oligouridine tail to pre-let-7 that subsequently blocks Dicer processing [47]. Further, the interaction of PUP-2 with Lin28 controls the stability of Lin28-blockaded let-7 pre-miRNA which suppress the action of Dicer and contribute to the Lin28-stimulated uridylation of let-7 pre-miRNA [48].

2.2. Regulation of miRNA let-7 by nuclear factor 90 and nuclear factor 45

Nuclear factor (NF) 90 and NF45 are the member of Drosha family, which is crucial for the production of pre-miRNA from pri-miRNA. Altered expression of NF90 and NF45 is found to be associated with the level of pri-miRNA. The NF90-NF45 complex is shown to bind with the majority of pri-miRNAs, including pri-let-7a-1 and has higher binding affinity than the DGC8-Drosha complex, which also binds to pri-miRNAs. Due to elevated binding affinity, NF90-NF45 complex attenuate the processing of pri-miRNA by the DGC8-Drosha complex. The NF90-NF45 have been shown to have higher binding affinity for pri-let-7a-1 than the other pri-miRNAs [49].

2.3. Regulation of miRNA let-7 by other factors

DNA methylation is considered to be one of the reason that alter miRNA let-7 expression [50–52]. The human let-7 gene is located on chromosome 22q13.31, which is known to be methylated by the DNA methyltransferases such as DNMT3B and DNMT1. The miRNA let-7a-3 is found to be methylated in lung samples. Interestingly the hypomethylation of let-7a-3 promotes the expression of miRNA and reduce the growth of lung adenocarcinomas cells [52]. Moreover, hypermethylation downregulated the let-7a-3 in epithelial ovarian cancer and associated with unfavorable prognosis [53]. Several factors act at the time of let-7 biogenesis and control the expression of let-7 via regulatory loops. These loops can be either Lin28-dependent or Lin28-independent. The Lin28-dependent regulatory feedback loop involves the NFkB-Lin28-let-7-interleukin (IL)-6- NFkB, and Lin28-let-7-Lin28 loops. The NFkB is shown to activate Lin28 transcription and reduces let-7 levels. Further, let-7 can inhibit IL-6 expression that can activate NFkB, and completing a positive feedback loop [54]. c-Myc, an oncogene is one of the target of let-7. The expression of c-Myc regulated by IMP1 which is believed to be negatively and directly regulated by let-7 [55,56]. Further, c-Myc was demonstrated to transactivate Lin28B, which inhibit let-7 expression. In addition, activation of Lin28B was found to associate with Mcg-mediated let-7 expression [57,58]. Moreover, let-7 can also affect Lin28 expression as the binding of let-7 to the 3’ UTR of Lin28 transcripts represses Lin28 expression [58]. Lin28 is believed to be a classical direct inhibitor of let-7, which create a double-negative regulatory loop for let-7. Alteration in regulatory circuits affects the expression of let-7 that can promote normal and abnormal responses. A single nucleotide polymorphisms (SNPs) in tumor suppressor miRNA is believed to be responsible for several malignancies [59,60]. A SNP of the Lin28 gene, rs3811463 is shown to be involved in downregulation of let-7 via the let-7-Lin28 double negative feedback loop. rs3811463 was therefore believed to be associated with breast cancer [61].

2.4. Mechanism of miRNA let-7 mediated response

The best explained mechanism of let-7 miRNA action is binding to the 3’ UTR of target mRNAs to alter their expression. Further, let-7 induces its effect when it was targeted to the 3’ or 5’ UTRs of mRNAs, suggesting that let-7 can act via binding to sites other than the 3’ UTR [62]. In addition, let-7 is capable to bind directly to coding regions to target mRNAs to alter its expression [63]. It has been suggested that let-7a can inhibit the translation of target mRNAs by binding and inhibiting the translating polyribosomes [64]. Deadenylation that is removal of adenylate group from protein is another process that can be exploited by let-7 to inhibit or decay

![Fig. 1. Signaling pathways involved in miRNA let-7 expression.](http://dx.doi.org/10.1016/j.ncrna.2016.10.003)
the translation of mRNA. However, deadenylation alone seems insufficient to participate in mRNA repression [65].

2.5. Signaling pathways targeted by miRNA let-7

Let-7 is one of the miRNA that targets multiple signaling pathways including Janus protein tyrosine kinase (JAK), signal transducer and activator of transcription 3 (STAT3) and c-Myc. These pathways are crucial for tumor cell growth and aggressiveness. By suppressing these oncogenic pathways let-7 act as a tumor suppressor.

2.6. Regulation of JAK-STAT3 pathway by miRNA let-7

The JAK is a member of the intracellular, non-receptor tyrosine kinases that mediates signals via JAK-STAT3 signaling pathway. Activated JAK promotes STATs activation, which transmits the information from extracellular chemical to the nucleus and induces the expression of genes involved in differentiation, proliferation, apoptosis, oncogenesis and immunity [66]. The JAK-STAT3 pathway is believed to be activated in several types of malignancies [67,68]. Interestingly, STAT3 was found to be a target of let-7a, which mediates cell proliferation in HepG2 cells [69]. It is speculated that let-7 may regulate the activity of cancer cells by targeting JAK-STAT3 signaling pathway.

2.7. Regulation of Myc oncogene pathway by miRNA let-7

Myc (c-Myc) is a transcription factor that plays an important role in cell cycle progression and apoptosis. This gene is usually activated in tumors [70]. Activation of Myc promotes cell growth, and survival by enhancing the synthesis of its target proteins, which are associated with cell cycle and apoptosis [71]. In addition the mutation in Myc gene have been reported in many cancers which causes this gene to be persistently expressed that leads to the altered expression of several genes which are involved in growth and aggressiveness of the cancer. Altered expression of Myc has been found in the cancers of colon [72], cervix [73] and breast [74]. Several reports have been suggested that let-7a down-regulated Myc mRNA and protein [34,75]. Further, it has been suggested that miRNA let-7 regulates Myc expression by binding to its 3’ UTR. However, let-7 has been found to regulate the cell cycle by altering the expression of several downstream proteins such as cyclin D1 and cyclin-dependent kinase (CDK) 6 that are the part of Myc oncogene signaling pathway [76,77].

2.8. miRNA let-7 and breast cancer

BC is one of the leading causes of cancer related death in women. The poor outcome of BC is attributed to the heterogenous nature and metastasis. Another mechanism that helps tumor cell to grow unchecked is the development of cancer stem cell (CSC) phenotype. The let-7 microRNAs that regulate the expression of multiple genes related to the metastasis and stem cell phenotype and attracted scientific community to develop targeted therapies against BC. In this section we briefly discussed the role of let-7 in BC metastasis and stemness.

2.9. Role of miRNA let-7 in breast cancer metastasis

Metastasis is a process in which cancer cell break away from the original site and travels the blood or lymphatic system to the other parts of body and form new tumors. Chemotaxis is believed to be a fundamental cause of metastasis in which external signals orient and attract tumor cells. Overexpression of certain receptors facilitates BC cells to get attracted and move to other site. CCR7 is one of the receptor that is found to be overexpressed in BC and participate in metastasis [78]. CCR7 is activated by binding chemokines CCL21 and CCL19 [79,80]. T cells utilize CCL21 to enter lymphoid tissues from circulation. As far as CCL19 is concerned, it is expressed by mature dendritic cells which activates T cells [81]. However, tumor cells exploit the conditions by expressing CCR7 that helps them to localize in lymph node after receiving the chemotactic signals from CCL19 or CCL21. miRNAs have been suggested to suppress the expression of numerous cancer-related genes that subsequently reduces tumorigenesis and metastasis in BC and several other cancers [82–84]. A study examined the roles of CCR7 and miRNA in breast cancer metastasis suggested that let-7 family binds participate in the process of metastasis [85]. Let-7a was found to influence the CCR7 down expression by targeting 3’UTR of CCR7, thereby downregulating BC cell invasion and migration. Similar results were confirmed in study performed using zebrafish embryo models. Let-7a, a member of family let-7 act as a tumor suppressor by regulating the expression of RAS and HMGA2 oncogenes [86–88]. Further, decreased levels of let-7a was found to associate with elevated RAS expression in lung squamous carcinoma [86].

2.10. Role of miRNA let-7 in breast cancer stemness

CSCs, a sub-population of tumor cells is believed to be largely responsible for the therapy resistance and unfavorable clinical outcome. miRNAs have been suggested to contribute in tumor initiation by regulating the properties of CSC, including de-

| S. No. | Type of cancer       | Target gene | Gene title                                      | References |
|-------|----------------------|-------------|------------------------------------------------|------------|
| 1     | Thyroid cancer       | SLC5A5      | Sodium iodide cotransporter or solute carrier   | [97]       |
|       |                      |             | family 5, member 5                              |            |
| 2     | Oral Squamous cell   | OCT4        | octamer-binding transcription factor 4          | [98]       |
|       | Carcinoma            |             |                                                |            |
| 3     | Ovarian Cancer       | KRAS        | Kirsten rat sarcoma viral oncogene homolog     | [99]       |
| 4     | Pancreatic Cancer    | STAT3       | Signal transducer and activator of transcription | [100]      |
| 5     | Neuroblastoma        | MYCN        | V-Myc Avian Myelocytomatosis Viral Oncogene     | [101]      |
|       |                     |             | Homolog                                        |            |
| 6     | Lung Cancer          | ITGB3       | integrin beta-3                                 | [102]      |
| 7     | Liver Cancer         | HMGA2       | High-mobility group AT-hook 2                   | [103]      |
| 8     | Prostate Cancer      | IL-6        | Interleukin 6                                   | [104]      |
| 9     | Endometrial Cancer   | Aurora-B    | Aurora B kinase                                | [105]      |
| 10    | Colorectal Cancer    | KRAS        | Kirsten rat sarcoma viral oncogene homolog     | [106]      |
| 11    | Gastric Cancer       | CMYC        | V-Myc Avian Myelocytomatosis Viral Oncogene a    | [107]      |
|       |                     |             | Derived Homolog                                 |            |
| 12    | Multiple Myeloma     | MYC         | V-Myc Avian Myelocytomatosis Viral Oncogene     | [108]      |
|       |                     |             | Homolog                                        |            |
| 13    | Burkitts Lymphoma    | MYC         | V-Myc Avian Myelocytomatosis Viral Oncogene     | [34]       |
|       |                     |             | Homolog                                        |            |
differention, self-renewal and therapy resistance [89,90]. Let-7 is emerged as a major regulator of CSC properties including self-renewal and tumor-seeding ability [91]. CSCs demonstrated recent down-regulation of let-7 expression in BC cells. Further, let-7 is shown to inhibit the self-renewal and de-differentiation capacity of BC cells by targeting several genes such as RAS and high mobility group AT-hook 2 (HMGA2) [92]. Further, in BC let-7 is found to suppress tumorigenicity and self-renewal capability by targeting H-RAS and HMGA2 [92]. Delivery of miRNAs in lung cancer using nucleic acid aptamers specific to the receptor tyrosine kinase oncogene Axil, conjugated with let-7g, which target HMGA2, showed effective inhibition of tumor growth [93,94]. Thus, combining let-7 with specific antibodies or aptamers against breast CSCs, might be a useful approach to improve the treatment of BC patients [95,96]. Considerable efforts have been made to improve the target specific delivery of miRNA, however, more research is required to improve the therapeutic efficacy and design of vehicles and methods for their delivery in vivo.

3. Conclusion

The research on miRNA have delivered several new aspects of therapeutics and crossed a long way since its discovery. Multiple parameters such as their small size and conserved sequence make them a potential candidate for drug development program. Furthermore, miRNA targeted downstream genes that function in numerous ways including growth, aggressiveness, and therapy resistance, thus targeting single miRNA can have multiple implications. As let-7 have shown multiple connections with metastasis and stemness of BC, the day is not far off when let-7 will be a good therapeutic target for the patients suffering from BC and other malignancies. In addition altered expression of let-7 family members have been shown to influence the self-renewal capacity of the CSCs (Table 1). However, the understanding of precise mechanism is required to gain more insights into the therapeutic efficacy of miRNAs.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2015, CA. Cancer J. Clin. 65 (2015) 5–29.
[2] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2016, CA. Cancer J. Clin. 66 (2016) 7–30.
[3] S.K. Deshmukh, S.K. Srivastava, A. Bhardwaj, A.P. Singh, N. Tyagi, S. Marimuthu, D.L. Dyess, V. Dal Zotto, J.E. Carter, S. Singh, Resistin and p-21 activated kinase 4 (PAK4) family members have been shown to influence the expression of in silico identified Bcell epitope of epsilon toxin of Clostridium perfringens D, causative agent of enterotoxaemia, Appl. Microbiol. Biotechnol. 88 (2010) 877–884.
[4] N. Siliprandi, F. Di Lisa, R. Menabue, Propionyl-L-carnitine: biochemical significance and possible role in cardiac metabolism, Cardiovasc. Drugs Ther. 19 (2005) 421–427.
[5] P. Hydbring, G. Badalian-Very, Clinical applications of microRNAs, F1000Research 2 (2013) 136.
[6] J.F. Barger, S.P. Nana-Sinkam, MicroRNA as tools and therapeutics in lung cancer, Respir. Med. 109 (2015) 803–812.
[7] N. Tyagi, S. Srara, S.K. Deshmukh, S. Singh, S. Marimuthu, A.P. Singh, Exploiting nanotechnology for the development of MicroRNA-based Cancer therapeutics, J. Biomed. Nanotechnol. 12 (2016) 28–42.
[8] T.W. Nilsen, Mechanisms of microRNA-mediated gene regulation in animal cells, Trends Genet. 23 (2007) 243–249.
[9] R.W. Carthew, E.J. Sontheimer, Origins and Mechanisms of miRNAs and siRNAs, Cell 136 (2009) 642–655.
[10] R.W. Carthew, E.J. Sontheimer, Origins and Mechanisms of miRNAs and siRNAs, Cell 136 (2009) 642–655.
[11] J. Takamizawa, H. Konishi, K. Yanagisawa, S. Tomida, H. Osada, H. Endoh, T. Harano, Y. Yatabe, M. Nagino, Y. Mimura, T. Mitsudomi, T. Takahashi, Reduced expression of let-7a microRNA in human lung cancers in association with shortened postoperative survival, Cancer Res. 64 (2004) 3753–3756.
MYC-induced growth in Burkitt lymphoma cells, Cancer Res. 67 (2007) 9762–9770.

X. He, Y. Yang, Y. Guo, Z.O. Cao, Z.W. Cui, T.C. Hu, L.B. Gao, Association of a let-7 XKR5 rs1724 polymorphism with the risk of breast cancer, Genet. Mol. Res. 14 (2015) 16913–16920.

N.S. Sokol, P. Xu, Y.-N. Jan, V. Ambros, Drosp hilica let-7 microRNA is required for remodeling of the neuromusculature during metamorphosis, Gen Dev. 22 (2008) 1591–1596.

E.E. Caygill, L.A. Johnston, Temporal regulation of metamorphic processes in Drosp hilica by the let-7 and mir-125 heterochronic microRNAs, Curr. Biol. CB 18 (2008) 966–970.

J.M. Thomson, J. Parker, C.M. Perou, S.M. Hammond, A custom microarray platform for analysis of microRNA gene expression, Nat. Methods 1 (2004) 45–50.

Y. Liao, X. Wei, M. Jin, Simultaneous presentation of acute myocardial infection and acute promyelocytic leukemia, Ann. Hematol. 85 (2006) 409–410.

C. Chang, J.T. Mendell, microRNAs in vertebrate physiology and human disease, Annu. Rev. Genomics Hum. Genet. 8 (2007) 215–239.

F.J. Pérez-Llarena, M. Cartelle, S. Mallo, A. Becerril, A. Pérez, R. Villanueva, A. Romero, R. Bonnet, G. Bou, Structure-function studies of arginine at position 276 in CTM-β-lactamases, J. Antimicrob. Chemother. 61 (2008) 792–797.

M.A. Newman, J.M. Thomson, S.M. Hammond, Lin-28 interaction with the BCL-2 family members Bcl-x and Bcl-2 inhibits let-7 maturation in mouse embryonic stem cells, Nat. Struct. Mol. Biol. 16 (2009) 1021–1025.

I. Heo, J.C. Joo, C. Kim, H.-Y. Youn, J. Han, V.N. Kim, TUT4 in concert with Lin28 suppresses microRNA biogenesis through pre-microRNA uridylation, Cell 138 (2009) 696–708.

N.J. Lehrbach, J. Armisen, H.L. Lightfoot, J.A. Chen, Barnholtz-Sloan, M.J. Reiter, G. Bloom, S.J. Kinne, C. Zhen, D.W. Cancer, J.M. Cunningham, G. Dagne, J. Ebbert-Syfrett, D. Fenstermacher, B.L. Fridley, M. Garcia-Closas, S.A. Gayther, W. Ge, A. Gentry-Maharaj, J. Gonzalez-Bosquet, E.L. Goode, E. Iversen, H. Jin, W. Kong, J. Laughlin, U. Menon, A.A.A. Monteiro, S.A. Morgan, P.D.P. Peto, Lin28, a new developmental cell-lineage marker, J. Cell. Sci. 124 (2011) 2692–2701.

A.-X. Chen, K.-Y. Yu, L. Fan, J.-Y. Li, C. Yang, A.-J. Huang, M.-Z. Shao, Germline genetic variants disturbing the let-7/LIN28 double-negative feedback loop after alterations of breast cancer susceptibility, PLoS Genet. 7 (2011) e1002259.

J. Piskounova, R.I. Gregory, Lin28 recruits the TUTase Zcchc11 to mediate the terminal differentiation of breast cancer cells, Cancer Res. 75 (2015) 7926–7976.

Y. Wang, Y. Lu, S.T. Toh, W.-K. Sung, P. Tan, P. Chow, A.Y.F. Chung, L.L.P. Jooi, Metastatic breast cancer: the potential of microRNA biomarkers for transition of cervical intraepithelial neoplasia to cervical cancer, Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc. 24 (2014) 643–648.

Y. Lou, W. Mai, J. Jin, Simultaneous presentation of acute myocardial infarction and acute promyelocytic leukemia, Ann. Hematol. 85 (2006) 409–410.

J. Forman, A. Legesse-Miller, H.A. Coller, A search for conserved sequences in coding regions reveals that the let-7 microRNA targets Dicer within its coding sequence, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 14877–14878.

S. Sillrett, J.H. Siadard, V.D. Martin, Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 9667–9672.

J.P. Hagan, E. Piskounova, R.I. Gregory, Lin28 mediates the terminal differentiation of breast cancer cells, Cancer Res. 75 (2015) 6783.

R.J. Leeman, V.W.Y. Lui, J.R. Grandis, STAT3 as a therapeutic target in head and neck cancer, Expert. Opin. Biol. Ther. 6 (2006) 231–241.

J.R. Lytle, T.A. Varco, J.A. Steitz, Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 14774–14779.

T.H. Beilharz, D.T. Humphreys, J.L. Clancy, R. Thermann, D.M. Westen, H.M. Hentze, T. Preiss, microRNA-mediated messenger RNA degradylation contributes to translational repression in mammalian cells, PLoS One 4 (2009) e7683.

R.J. Leeman, V.W.Y. Lui, J.R. Grandis, STAT3 as a therapeutic target in head and neck cancer, Expert. Opin. Biol. Ther. 6 (2006) 231–241.

J.R. Lytle, T.A. Varco, J.A. Steitz, Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 14877–14878.

S. Nottrott, J.M. Simard, J.D. Richter, Human let-7a miRNA blocks protein production on actively translating polyribosomes, Nat. Struct. Mol. Biol. 13 (2006) 1108–1114.

A. Thammiah, K. Jayaram, Role of let-7 family microRNA in breast cancer, Non-coding RNA Research (2016), http://dx.doi.org/10.1016/j.ncrna.2016.10.003

Please cite this article in press as: C.K. Thammaiah, S. Jayaram, Role of let-7 family microRNA in breast cancer, Non-coding RNA Research (2016), http://dx.doi.org/10.1016/j.ncrna.2016.10.003
A.I. Damanakis, S. Eckhardt, A. Wunderlich, S. Roth, T.T. Wissniowski, C.L. Esposito, S. Catuogno, V. de Franciscis, Aptamer-mediated selective delivery of microRNA to cancer cells, J. RNAi Gene Silenc. Int. J. (2015) 27 1070.