



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.

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1. Introduction

Breast cancer (BC) is most frequently diagnosed cancer and remains one of 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 pathogen [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 mRNAs 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]. Abnormal expression of miRNAs such as *let-7* has been reported in several malignancies including BC. In year 2000 Reinhart et al. demonstrated that *let-7* miRNA alter the phenotype of nematode and regulates the development of *Caenorhabditis elegans* [30]. In human, 10 members of the *let-7* family have been identified, including *let-7a*, *let-7b*, *let-7c*, *let-7d*, *let-7e*, *let-7f*, *let-7g*, *let-7i*, *miR-98* and *miR-202*. In normal physiological conditions *let-7* is primarily involved in gene regulation, cell adhesion and muscle formation. Accumulating evidence suggests that *let-7* is downregulated in numerous types of cancer, including gastric tumors [31], colon cancer [32], lung cancer [33], Burkitt's lymphoma [34] and BC [35]. The *let-7* family of miRNA is associated with apoptosis, proliferation and invasion of cancer cells. Further, *let-7* regulates several signaling pathways that are crucial for the biological characteristics of tumor cells. In this review article we have explored the possible factors associated with *let-7* expression and its mechanisms of action. Further, we described the target of *let-7* that are important for BC cell growth, aggressiveness and explored the benefits of targeting *let-7* to control the BC

Abbreviations: miRNAs, MicroRNAs; BC, breast cancer; IL-6, interleukin-6; 3' UTRs, 3' untranslated regions; SNPs, single nucleotide polymorphisms; NF, nuclear factor; JAK, Janus protein tyrosine kinase; STAT3, signal transducer and activator of transcription 3; CSC, cancer stem cell.

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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 binding 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 Droscha/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 blockage of *let-7* processing in mouse embryonic stem cells [46]. *Lin28* recruit TUT4 to *pre-let-7* by recognizing tetranucleotide 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 DGCR8-Drosha complex, which also binds to pri-miRNAs. Due to elevated binding affinity, NF90-NF45 complex attenuate the processing of pri-miRNA by the DGCR8-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 NFκB-*Lin28-let-7*-interleukin (IL)-6-NFκB, and *Lin28-let-7-Lin28* loops. The NFκB is shown to activate *Lin28* transcription and reduces *let-7* levels. Further, *let-7* can inhibit IL-6 expression that can activate NFκB, 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 *Myc*-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 involved in 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

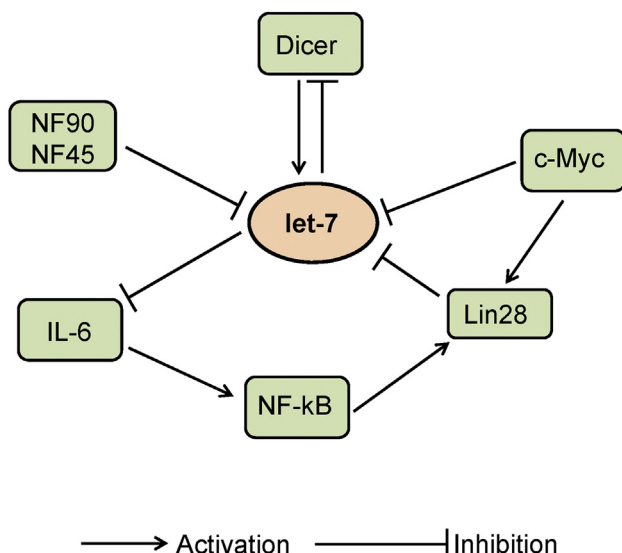


Fig. 1. Signaling pathways involved in miRNA *let-7* expression.

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 in 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. CXCR7 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 for 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-

Table 1
miRNA *let-7* family target genes in various cancers.

S. No.	Type of cancer	Target gene	Gene title	References
1	Thyroid cancer	SLC5A5	Sodium/iodide cotransporter or solute carrier family 5, member 5	[97]
2	Oral Squamous cell Carcinoma	OCT4	octamer-binding transcription factor 4	[98]
3	Ovarian Cancer	KRAS	Kirsten rat sarcoma viral oncogene homolog	[99]
4	Pancreatic Cancer	STAT3	Signal transducer and activator of transcription 3	[100]
5	Neuroblastoma	MYCN	V-Myc Avian Myelocytomatosis Viral Oncogene Homolog	[101]
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 Derived Homolog	[107]
12	Multiple Myeloma	MYC	V-Myc Avian Myelocytomatosis Viral Oncogene Homolog	[108]
13	Burkitts Lymphoma	MYC	V-Myc Avian Myelocytomatosis Viral Oncogene Homolog	[34]

differentiation, self-renewal and therapy resistance [89,90]. *Let-7* is emerged as a master regulator of CSC properties including self-renewal and tumor-seeding ability [91]. CSCs demonstrated CD44+/CD24-/low antigen phenotype in mammosphere culture conditions and treatment with anti-cancer reagents and have significant 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 *Axl*, 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. Further, 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 several other malignancies (Table 1). However, the understanding of precise mechanism is required to gain more insights into the therapeutic efficacy of miRNAs.

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