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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 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 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 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].

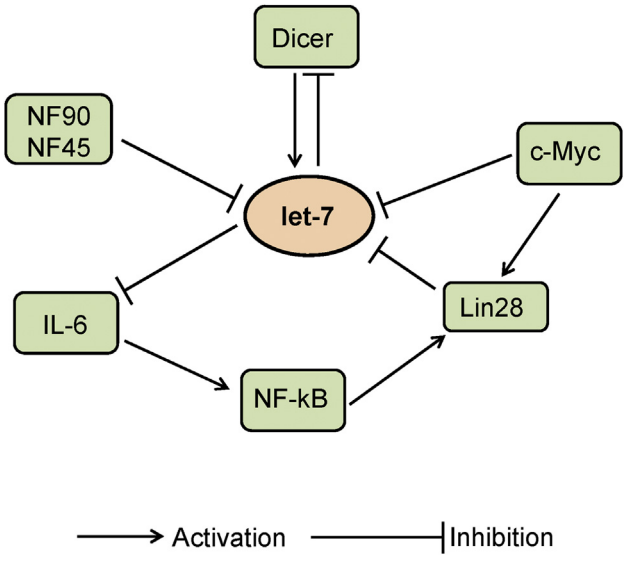

Fig. 1. Signaling pathways involved in miRNA *let-7* expression.

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 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