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Review

The role of oncomirs in the pathogenesis and treatment of breast cancer

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ABSTRACT

Breast cancer, the most common cancer among women, is a heterogeneous and complex disease, which detail of its precise progression mechanisms is less understood. So, an improved comprehension of the precise molecular mechanisms leading to disease progression and design of effective targeted therapies are required for patients with breast cancer. MicroRNAs demonstrate an uncovered class of small and endogenous non-coding RNAs and play an important role in the normal biological processes, including cell differentiation, proliferation and apoptosis. Some miRNAs, known as oncomiR, show different expression levels in cancer and are capable to effect on cellular transformation, carcinogenesis and metastasis and are characterized by high expression levels in tumors compared to normal tissues. Therefore, oncomiRs can be considered as prognostic biomarkers and therapeutic targets in different types of cancers. Moreover, the utilization of oncomiRs as therapeutic targets for cancer is promising. Accordingly, there is evidence which implies an important role of various oncogenic microRNAs in immunopathogenesis of breast cancer. In this review we will discuss about the role of various oncomiRs such as miR-21, miR-155, miR-10b, and miR-221/222 in the pathogenesis and treatment of breast cancer.

Contents

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1. Introduction

Breast cancer is a main cause of cancer death among women in industrialized countries, regardless advances in early detection and treatment. Breast cancer led to death of about 88.886 and 39.620 women at 2013 in European and American women, respectively [1,2]. Gene expression profile in breast cancer has contributed substantially to our understanding of disease heterogeneity at a molecular level, purifying taxonomy according to simple measures such as histological type, tumor grade, lymph node status and the presence of predictive markers such as oestrogen receptor and human epidermal growth factor receptor 2 (HER2) to a more advanced classification consist of luminal A, luminal B, basal-like, HER2-positive and normal subgroups [3].

Furthermore, technological advances, especially genomics and proteomics, have suggested the feasibility to make better treatment tailoring throughout the recognition of new targets for anticancer therapy. MicroRNAs are involved in several processes related to Breast cancer biology, such as apoptotic, pro-angiogenetic, signal transduction, cell cycle, and metastatic pathways. These molecules are a recently identified class of small and endogenous non-coding RNAs [4]. MiRNAs play an important role in regulating gene expression and the phenotype of tumor cells as they affect cell proliferation [5–7], cell cycle progression [8–10], survival [11,12], invasion [13–15], cell differentiation [16,17], and morphogenesis [18]. Recent studies have been shown that miRNAs are involved in the pathogenesis and treatment of various types of cancer, including breast cancer. In this review we discuss about the role of various MicroRNAs that called oncomiRs and their role in the pathogenesis and treatment of breast cancer.

2. MicroRNAs history

MicroRNAs are a family of 19–24-nucleotide small RNAs that had discovered in 1993 by Lee et al. [19] in the nematode *Caenorhabditis elegans* [20]. In *C. elegans*, cell lineages have different characteristics during 4 dissimilar larval stages (L1–L4) [21]. The downregulation of LIN-14 protein was found to be crucial for the promotion from the first larval stage (L1) to L2. As well, the down regulation of LIN-14 was discovered to be dependent on the transcription of a second gene named lin-4. Remarkably, the transcribed lin-4 was not translated into a biologically active protein. Instead, it gave rise to 2 small RNAs about 21 and 61 nucleotides in length. The longer sequence made a stem-loop structure and acted as a precursor for the shorter RNA. The smaller RNA had antisense complementarity to multiple sites in the 3′ UTR of lin-14 mRNA and binding between these complementary sites diminished LIN-14 protein expression without leading to any remarkable change in its mRNA levels. This new strategy of regulating gene expression was first thought to be a phenomenon exclusive to *C. elegans* [19–22]. A small RNA, let-7, was necessary for the progression of a later larval stage to adult in *C. elegans* [23,24]. Importantly, homologues of this gene were eventually found in many other organisms, including humans [25].

According to these information multiple laboratories cloned various small RNAs from humans, flies, and worms. These RNAs were noncoding, about 19–24 nucleotides in length and originated in a longer precursor with stem loop structure [26]. The recognition of these small RNAs, now called MicroRNAs, led to intense research aimed at determining new members of this family [20].

3. Biogenesis of microRNA

MiRNAs regulate gene expression post transcriptionally but do not encode any proteins. Most miRNA loci are located in non-coding intronic transcription regions, but some are found in exonic regions [27]. Two processing pathways promote MiRNA maturation in animals. In the first, the nascent MiRNA transcripts (pri-MiRNA) are processed into ~70–120 nucleotide precursors (pre-MiRNA). Pri-MiRNAs are located in introns of host genes, including both protein-coding and non-coding genes, and might be transcriptionally controlled through their host-gene promoters [28], subsequently, precursors are cleaved to generate ~19–24 nucleotide mature MiRNAs [29]. Briefly, MiRNA coding transcripts are initially transcribed by RNA polymerase II as long primary miRNAs (several hundred nucleotides long) with a 5′ guanosine cap and a 3′ poly adenylated tail. These miRNAs are then processed into 70–120-nucleotide-long precursor RNAs (pre-MiRNAs) by a multi protein complex called Microprocessor [20]. The consecutive cleavages of MiRNA maturation are catalyzed by two RNase-III enzymes, Drosha and Dicer [30,31]. Both are double strand (ds) RNA-specific endonucleases that generate 2-nucleotide-long 3′ overhangs at the cleavage site. Drosha is a 160 kDa nuclear RNase-III enzyme that is highly conserved in animals but not in plants [32] and contains two tandem RNase-III domains, including a dsRNA binding domain and an amino-terminal segment with unknown function [31]. To form the functional Microprocessor complex, Drosha dimerizes with another dsRNA binding protein, called DiGeorge syndrome critical region gene 8 (DGCR8) or Pasha [33–36]. Regardless of the diverse primary sequences and structures of pri-MiRNAs, Drosha cleaves these into ~70-bp pre-miRNAs that consist of a defective stem-loop structure [31]. By exportin 5 (Exp-5), a Ran-dependent nuclear transport receptor protein, the transcribed pre-miRNA with a typical 5′ phosphate and ~2-nucleotide 3′ overhang is then exported into the cytoplasm [37,38]. In the cytoplasm, the pre-MiRNAs are eventually processed into mature 19–24 nucleotide-long duplexes by another RNase III enzyme, Dicer-1 [39]. Dicer includes a helicase domain, a DUF283 domain, a PAZ (Piwi–Argonaute–Zwille) domain, two tandem RNase-III domains and a dsRNA-binding domain (dsRBD) [40]. The 5′ end stability and thermodynamic asymmetry of the duplex assess the segregation of 2 miRNA strands. The miRNA strand with the unstable base pairing at the 5′ end normally acts as the guide strand, whereas the strand with the stable base pairing at the 5′end (known as the passenger or miR strand) is usually degraded. The guide strand in association with the RNA binding proteins, that contain trinucleotide repeat-containing gene 6A (TNRC6A), and catalytic Argonaute (AGO) proteins form a microribonuclear protein complex (miRNP) called RNA-induced silencing complex (RISC) [41]. This strand guides the complex toward the target mRNA through sequence complementarity and leads to its translational repression. Therefore, miRNAs