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# Pathological Function and Clinical Significance of Microrna-10b in Cancer

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## Abstract

Micro RNAs, the endogenous non-coding small RNAs are found involved in cancer pathogenesis. Identification of the miRNA signature in cancer and understanding the underlined regulatory mechanism provide information for clinical decision. Increasing evidences show that miR-10b plays important role in cancer progression and metastasis, thus it may be a therapeutic target for cancer control. Moreover, the alternations of miR-10b expression in malignant diseases provide great potential to use this molecule as a cancer biomarker for early detection, disease assessment or therapeutic monitoring. In this article, we review current knowledge about the cellular function of miR-10b, and discuss its clinical significance and potential application in cancer.

**Keywords:** microRNA-10b; Clinical significance; Cancer

## miRNA Discovery, Biogenesis, Action Mechanism and Detection

MicroRNAs (miRNAs) are small, non-coding RNA molecules encoded in the genomes, with length in range of 18-25 nucleotides. These molecules are transcribed from hairpin-loop primary ribonucleotides (pri-miRNA) by RNA polymerase II [1,2]. Pri-miRNAs are processed by RNase-III family enzyme, Dorsha, and then become 70nt precursor miRNA (pre-miRNA). The pre-miRNA is exported out to the cytoplasm by Exportin-5, in a Ran-GTP-dependent manner. In the cytoplasm, the pre-miRNA is cleaved by Dicer to generate a 20-bp duplex intermediate [2,3], and further unwound to mature miRNA. In order to control target gene expression, the single strand mature miRNA must associate with the RNA-induced silencing complex (RISC) [4]. Once miRNA incorporates into RISC, the miRNA guides the complex to its target by base-pairing with the target mRNA.

The first identified miRNA is lin-4, which has been discovered in Caenorhabditis elegans [5]. This 22 nucleotide small RNA is shown to interact with the 3′ un-translated region (3′-UTR) of the lin-14 mRNA and to repress its expression [6,7]. It is now clear that miRNAs regulate their targets by inhibition of protein synthesis or by direct cleavage of the target mRNA, according to the degree of complementarities with their targets 3′-UTR region. When miRNA is perfectly complementary binding, the target mRNA will be degraded, whereas when partial complementary binding, target protein translation will be blocked [8]. In the past decade, novel miRNA molecules were discovered across in many sapiens. Till now, there are 1872 precursors, and 2578 mature miRNAs sequence in Homo sapiens listed in miRBase (release 20). Through miRNA target predictions, it is estimated that up to 30% of the genes are under control by currently known miRNAs in mammals [9,10]. Each mammalian miRNA regulates ~200 target genes in average through interaction with the seed sequences of the complementary target sites [9,11]. All of these findings suggest that miRNA has become a big family of gene regulators. Furthermore, detection of mature miRNAs is another challenge because of small size and the sequence similarity among various members. Before, northern blot was considered a gold standard for miRNA detection. However, time consuming and less sensitivity of this assay was shown [12]. Several approaches are improved for miRNAs detection, including quantitative reverse transcription PCR (RT-PCR), hybridization-based method and next generation sequencing [13]. The detection method improvement contributes to accomplish miRNA studies in disease and in clinical application.

## The Physiological Functions of miRNAs in Cancer

Accumulating studies have strongly supported the roles of miRNAs regulating in various crucial cellular processes, including cell proliferation [14], apoptosis [15], development [16], differentiation [17] and metabolism [9]. In addition, miRNAs alteration through disrupting the homeostasis of biological process often leads to many human diseases, such as cancer [10,18,19]. There are 50% miRNA genes identified localized in cancer associated genomics region (CAGR) or fragile sites suggesting the correlation between miRNA and cancer disease [11]. Evidences demonstrated that miRNAs could act as oncogenes or tumor suppressive genes to participate in tumorigenesis [20,21]. Over-expression of a miRNA that targets to a specific tumor suppressive gene could result in loss of the molecular protective factor. In contrast, less expression of a miRNA targeting to a specific proto-oncogene could lead to excessive amount of the oncogenic protein expression [22-24]. Besides, increasing reports reveal that miRNAs through regulating

Cancer stem cells (CSCs) and the epithelial-mesenchymal transition (EMT) play pivotal roles in cancer pathogenesis [25]. The first tumor suppressive miRNA was reported by the observation of the under-expression of miR-15a and miR-16-1 in 68% of chronic lymphocytic leukemia patients (CLL) [26]. Thereafter, several target genes, such as B-cell CLL/lymphoma 2 (BCL2), cyclin D1 and WNT3A were identified regulated by miR-15a and 16-1 in CLL, prostate cancer and gastric cancer patients [27-29]. On the other hand, miR-21 is one of well recognized oncogenic microRNA that has been found over-expressed in various cancers, including breast [30-33], gastric [34], colorectal [35] and hepatocellular cancers [32]. Tumor suppressive genes, such as TPMI, PTEN, PDCD4 and MARCKS were found as targets of miR-21, demonstrating oncogenic functions of this molecule in various molecular mechanisms [36-38]. Similarly, miR-10b has been widely reported altered expression in various types of cancers, including breast [39-42], ovarian [43], bladder [44], esophageal [45], pancreatic [46], gastric [47], oral cancer [48] and human glioma [49]. Because of up-regulation in most cancers, miR-10b is appearing playing an oncogenic function. Here, we summarize the reports and point out the pathological significance of miR-10b in malignant disease.

## Role of microRNA-10b in Cancers and the Molecular Regulatory Mechanism

The miR-10b is located on human chromosome 2q31, between Hoxd4 and Hoxd8 genes in genome sequence [50]. In 2005, miR-10b was first discovered associated with cancer, by over-expression in glioblastoma cells through microarray analysis [51]. At the same year, through comparing microRNA profiling between cancer and normal tissue samples, this miRNA was also found altered expression in breast cancer. The potential targets were identified, as FLT1, BDNF and SHC1 [52]. The report of miR-10b by Ma et al. [39] further draws attention. They found that miR-10b was highly expressed in metastatic cancer cells than either primary human mammary epithelial cells (HMECs) or spontaneously immortalized MCF-10A cells [39]. In accord with the expression pattern in cultured cells, breast carcinoma tumor cells obtained from metastasis-free patients showed lower level of miR-10b expression [52]. In contrast, miR-10b was elevated in primary tumors obtained from metastasis-positive patients [39,52] concluded that miR-10b participates in the metastatic process rather than the tumor initiating stage during the development of breast cancer [39]. Thereafter, many molecular findings further supported the significance of miR-10b in cancer. It was found that miR-10b inhibited the synthesis of HOXD10 which facilitated the expression of pro-metastatic genes (RhoA/RhoC, urokinase plasminogen activator receptor, α3-integrin, and MT1-MMP), leading to cell migration and invasion in breast cancer [39,41,53]. Similarly, miR-10b down-regulated syndecan-1, which induced the expressions of transcription factors (AML1/RUNX1 and ATF2), resulting to cell-cycle progression and metastasis [54]. Furthermore, miR-10b may modulate metastasis in breast cancer through E-cadherin associated mechanism or TGF-induced epithelial-mesenchymal transition [55,56]. Aside from breast cancer, miR-10b also participates in the progression of other malignant diseases. Inhibition of miR-10b through inducing neurofibromin and RAS signaling resulted in the suppressions of cell proliferation, migration and invasion in neurofibromatosis type 1 malignant peripheral nerve sheath tumors (MPNSTs) [57]. In gastric cancer, miR-10b through targeting to HOXD10 stimulated RhoC and AKT phosphorylation to promote cell invasion [47]. In pancreatic cancer, miR-10b enhanced EGFR phosphorylation, ER1/2 activation, and EGF-induced cell invasion through targeting to Tat-interactin protein 30 (TIP30) [46]. In nasopharyngeal cancer, latent membrane protein-1 in Epstein-Barr virus induced twist activation, resulting to up-regulation of miR-10b expression to enhance cancer metastasis [58]. In bladder cancer, the regulatory mechanisms of miR-10b/KLF4/E-cadherin and miR-10b/HOXD10/MMP14 were found to promote cell invasion [44]. In head-neck cancer, miR-10b facilitated cell migration and invasion, while minimal effects on cell growth or stress response [48]. Most studies revealed that miR-10b participated in metastasis regulation. Nevertheless, it was also found involved in glioma cell growth and cell death [49]. In glioblatoma, miR-10b regulated cell proliferation and apoptosis by targeting to cell cycle inhibitor (BCL2L11/Bim) and proapoptotic genes (TFAP2C/AP-2g, CDKN1A/p21, and CDKN2A/p16) [59]. Collectively, miR-10b plays oncogenic function in common cancers. However, the molecular mechanisms may be very dependent on specific tissue type.

## Clinical Significance and Potential Applications of miR-10b in Cancer

Therapeutic application of miRNA may be used by two ways: miRNA antagonists and miRNA mimics. Treatments of miRNA antagonist or miRNA mimic may lead to gain- or loss-of the specific miRNA in the diseased tissues. Recent works showed that miRNA mimics have been developed in the stage of the preclinical trial for solid tumor treatment. For example, therapeutic delivery of let-7 mimic which targets to oncogene RAS led to a robust inhibition of tumor growth in xenografted mouse or KRAS-G12S transgenic mouse [60]. Another approach by targeting of metastatic- suppressive miRNAs could serve as a novel strategy to inhibit cancer spread. Since miR-10b plays a crucial role in regulating metastatic behavior, investigators intend to develop agents directly against this molecule. It has shown that systemic treatment of miR-10b antagonist to tumor-bearing mice markedly suppressed the formation of lung metastatic nodules [61]. Another design by a nanodrug, which features a nanoparticle with RGD (tripeptide arginine-glycine-aspartic acid) decorated with locked nucleic acid oligonucleotides also showed a therapeutic ability. This anti-miR-10b nanodrug prevented the metastasis process in orthotopic tumor bearing mice [62].

The emergence of miRNAs as mediators of gene regulation suggesting these molecules could serve as biomarkers for diagnosis or prognosis. It has shown that miR-10b expression determined by in situ hybridization is highly correlated with cancer occurrence, therapy response, and prognosis in pancreatic ductal adenocarcinoma [63,64]. Recently, circulating miRNAs, which can be detected in the body fluids, as in saliva, urine and plasma, are thought to serve as minimally invasive biomarkers

[65, 66]. MiR-10b has been reported possessing high potential of cancer marker. For example, the circulating levels of miR-10b, miR-34a and miR-155 correlated with the metastatic status in breast cancer [67]. Another report showed that the combination of circulating miR-10b and miR-373 helps to assess lymph node status of breast cancer [68]. Similarly, serum miR-10b was also reported over-expressed in the breast cancer patients with bone metastasis [69]. Collectively, miR-10b may be used as biomarker to monitor metastatic status of breast cancer. Furthermore, the increasing level of miR-10b was also found in colorectal cancer with higher staged, indicating the potential of this molecule as a biomarker for aggressive malignant disease [70]. Nevertheless, another association of miR-10b was also reported in other cancer types. In esophageal carcinoma, the elevated expression of miR-10b was found in 95% of the cancer tissues compared to the normal counterparts, while without clinical correlation with metastatic status [45]. Similarly, up-regulation of miR-10b in plasma was found in approximately 90% of the patients with oral cancer, and serving high discriminative power with normal subjects (AUC=0.932). Furthermore, this elevation of miR-10b was also significantly higher in the plasma of patient with oral precancer lesions, suggesting the potential use of miR-10b as an early detection marker for oral cancer [48].

## Conclusions

Through understanding of the mechanism of miR-10b in pathological function provides the novel strategy for clinical applications. Increasing evidences have demonstrated the important role of miR-10b during cancer progression, especially on metastasis. Using miR-10b antagomir to regulate multiple down-stream target genes may serve an effective therapeutic approach. Furthermore, the association between miR-10b expression and clinical pathological status suggest the potential use of this molecule as biomarker in various cancers. To better detection of miR-10b alteration in body fluids should provide minimal invasive tool for cancer diagnosis, disease assessment, or therapeutic monitoring. In summary, miR-10b plays an important role in cancer progression, and significantly different in different status of diseases. Summarizing the carcinogenic significance of miR-10b would further lead to translation impacts of applying this molecule in cancer management.

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