Editorial

Small Things, Big Responses

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''Small is beautiful'' is a popular proverb. But, small is powerful and has big responses which can be well apprehended in connection with role of microRNA (miRNA or miRs) in cancer biology. MicroRNAs are small, endogenous, non-coding RNAs with 19-24 nucleotides in length regulating post-transcriptional gene expression [1]. Normally, these control many biological processes including growth, development, cellular metabolism and body immunity during patho-physiological conditions. Under abnormal condition, miRNAs express aberrantly and may act as oncogenes, tumor suppressors, or metastasis regulators. Multiple factors including malfunctioning of the miRNA processing machinery, mutation of oncogene due to positional effects, and epigenetic mechanisms contribute a lot to the complex miRNA-mediated gene network misregulation followed by tumorigenesis and metastasis [2].

It has been reported that miRNAs are well conserved in both plants and animals. MicroRNAs were first discovered as a developmental regulator of *Caenorhabditis elegans* in 1993 [3]. Majority of human miRNAs reside in intergenic regions or within the introns of genes and are transcribed by RNA polymerase II in the nucleus of a cell to produce primary miRNA (pri-miRNA), which consists of a 5′-cap, at least one ~70-nucleotide hairpin structure and a 3′-poly(A) tail and sequences along the hairpin structure. Pre-miRNAs are transported to the cytoplasm by exportin 5, and further processed by the ribonuclease III enzyme Dicer, to produce a mature miRNA strand and its complementary miRNA strand. At the post-transcriptional level. miRNAs become more active and regulate the expression of protein-coding genes. It has been estimated that 30% of the human genome are regulated by miRNAs. Currently, near about 2,578 mature miRNA sequences are processed from

1872 isolated human miRNA precursor genes (https://www.mirbase.org), many of them with unknown functions. The abundance of these small yet powerful RNAs with diversified functions make miRNAs an exciting class of regulatory biomolecules [4]. Most important fact is that differential expression pattern of miRNAs are well observed in various cancers of human being. Therefore, miRNAs could be used as potential biomarkers in prognosis, diagnosis and cancer therapy.

Recently, it has been evident that aberrant regulation of miRNA can act as either an oncogene and/ or a tumour suppressor gene (TSG) in tumorigenesis and has been observed to be associated with various malignancies. A potential oncogenic role for miR-21 has been well evidenced by various workers from breast, cervix, colon, lung, pancreas, stomach, ovary, prostate, oral cavity, head and neck oncology. Abnormal expression of miR-21 in glioblastoma is a common occurrence. In addition to miR-21, miR-95 has also been found to be abnormally expressed in cancer stem-like cells associated with radio-resistance of lung cancer. Okugawa *et al*. (2014) demonstrated for the first time that up-regulation of miR-21 in colorectal cancer (CRC) tissues was directly associated with the serum levels in a large cohort samples. This finding not only showed that miR-21 was secreted from CRC cancer cells but also confirmed that there was a positive correlation between tissue and serum with respect to miR-21 expression [5].

Costa *et al*. (2010) have observed that aberrant miRNA expression levels are directly linked with both facilitating and abrogating the tumorigenic process. They do so through their ability to control the expression of thousands of protein-coding and non-coding

genes, and through their ability to regulate transcription of genes via promoter-associated RNAs (paRNAs) [6]. Overexpression of miRNAs, such as miR-17–92, may turn them to oncogenes and promote carcinogenesis by negatively regulating TSGs which control either cell differentiation or apoptosis. However, underexpression of miRNAs, such as, let-7 acts as TSG and inhibits cancers by regulating oncogenes that control either cell proliferation or cell death. Alterations in the human 13q14 genomic region containing mir-15a and mir-16 are present in most human chronic lymphocytic leukaemia (CLL) leading to a decrease in mature miR-15a and miR-16 levels. Deactivation or loss of 13q14 occurs frequently in other malignancies including mantle cell lymphoma, multiple myeloma and prostate cancer. Loss of miR-15a and miR-16 correlates with Bcl2 over expression and heterogenous expression of these miRNAs leads to down regulation of the endogenous proteins. miR-140-5p has been confirmed to be a tumor suppressor in human breast cancer. However, the potential molecular mechanism of miR-140-5p in breast cancer invasion and angiogenesis has not been well understood. Lu *et al*. (2017) reported that miR-140-5p inhibited the tumour invasion and angiogenesis of breast cancer cells both in vitro and in vivo by targeting VEGF-A. Furthermore, the mRNA amount of miR-140-5p was decreased in the breast cancer clinical samples and breast cancer with metastasis compared with the corresponding adjacent normal tissues and cancer without metastasis [7]. Thus, miR-15a, miR-16, and miR-140-5p are likely to be the *bona fide* TSGs and play a vital role during human carcinogenesis.

Three important biological fluids, such as blood, urine, saliva-have been used for the diagnosis of many diseases including cancer. Currently, the discovery of circulating miRNA in these body fluids warrants the attention of researchers. Due to their strong stability, miRNAs are easily detectable in body fluids. Differential expression profiles of these extracellular miRNAs in response to different patho-physiological conditions of the body signify their prognostic and diagnostic utility. The enigmatic roles of circulating miRNAs are also directly correlated with the cancer-type specificity. For instance, miR-92a, which was reported to be a plasma-based diagnostic marker in CRC, revealed the feasibility of exploiting plasma-based potential biomarkers in breast cancer and coronary artery disease. Findings of El-Gewely *et al*. (2016) indicate that down regulation of miR-143, miR-193b and miR-451 are well observed among meningioma cases. They also opined that down-regulation

of miR-21, and over-expression of miR-34a, miR218, PTEN and E-cadherin (CDH1) could explain the benign nature of meningiomas (grade I and II) and represent barriers for grade I and II tumors from malignant progression [8]. Son *et al*. (2017) have studied on the effects of radio-sensitivity in low-grade gliomas (LGGs) and reported that patients with upregulated miR-10a expression had a higher mortality rate and shorter overall survival (OS) time, whereas patients with downregulated miR-204 expression had a lower mortality rate and longer OS time. These miRNAs could therefore act as clinical biomarkers for LGG prognosis and diagnosis [9].

Upregulation of circulating miR-200 family members and significant downregulation of miR-132, miR-26a, let-7b, and miR-145 miRNAs are observed in the serum of ovarian cancer patients. Over-expression of circulating miR-21 has been found as an independent prognostic factor for both breast and lung cancer. Wu *et al*. (2016) revealed the important molecular mechanism by which miR-608 inhibits proliferation and induce apoptosis in human osteosarcoma cells [10]. Although, miR-197 is upregulated in lung, liver, and thyroid cancers, Ahn *et al*. (2017) reported that miR-197 expression is inversely correlated with programmed cell death ligand-1 (PD-L1 expression. The aggressive features of oral squamous cell carcinoma (OSCC), including high stage, angiolymphatic invasion, perineural invasion and death were associated with tumour-infiltrating lymphocytes (TILs) depletion. High T stage (T4) tumours also had low PD-L1 but had high miR-197 expression [11]. Wong *et al*. (2008) detected the presence of miR-184 in the plasma of 80% of patients with tongue squamous cancer (all stages) compared to 13% of healthy patients [12]. In the saliva of patients with OSCC, miR-125a and miR-200a were significantly under-expressed compared to controls [13]. Moreover, miR-31 was observed to be upregulated in both saliva and blood plasma of oral cancer patients [14]. Clague *et al*. (2010) also reported that there was a direct correlation between one variant allele of miR-26a and an increased risk to develop premalignant oral lesions [15].

The miRNAs are also associated with epigenetic traits called epi-miRNAs which influence a lot in biological arena. These epi-miRNAs can also alter the epigenetic landscape of cancer cells. The cancer 'epigenome' is characterized by global and gene-specific changes in DNA methylation, histone modification patterns and chromatin-modifying enzyme expression profiles, which impact gene expression in a heritable way. The first epi-miRNAs were

identified in a lung cancer study where miR-29 family (miR-29A, miR-29B, and miR-29C) was shown to target and downregulate de novo DNA methyltransferases (DNMT3A and DNMT3B). Additionally, miR-29B has been shown to induce global DNA hypomethylation and tumour suppressor gene re-expression in acute myeloid leukemia by targeting directly DNMT3A and indirectly the DNMT (DNMT1). This led to demethylation of CpG islands in the promoter regions of tumor-suppressor genes, allowing their reactivation and a loss of the cell's tumorigenicity [16]. In one way, miRNA expression can be altered by DNA methylation or histone modifications in cancer cells, but miRNAs can also regulate components of the epigenetic machinery, therefore, indirectly contributing to the reprogramming of cancer cells.

Metastasis-the ultimatum phase of cancer development has also not been escaped from the miRNAs intervention. Metastasis-regulatory miRNAs (metastamiRs) promote or inhibit cancer metastasis, These metastamiRs have been found to govern both cell-intrinsic and cell-extrinsic processes of the tumour microenvironment through various mechanisms, including regulation of migration, invasion, colonization, cancer stem cell formation, and epithelial-mesenchymal transition [17].

Recent evidences indicate that dietary factors also play an important role in the process of carcinogenesis through modulation of miRNA expression, Genistein- an isoflavone isolated from soybean, has been found to be a potent antitumor agent. In association with miR-16, genistein can potentially modulate the biological effects of miRNAs [18]. A chief constituent of Indian spices, Curcumin (diferuloylmethane), a naturally occurring flavanoid and proapoptotic compound derived from the rhizome of *Curcuma longa*, has been shown to have anticancer effect in various cancers [19]. More interestingly, it has also been evident that plant miRNAs are found in human and animal serum and that they are primarily acquired via food intake [20]. Exosome/microvesicle-mediated delivery of miRNAs, acquired via food intake or taken up by cells directly, could be a novel tool for cancer therapy. However, the isolation and quantification of circulating miRNAs remains a challenging task. RT-PCR method has been widely used to detect miRNAs from either tissue samples or serum samples. In recent years, microarray-based technique and next-generation sequencing (NGS) have also been widely used to detect expression profiles of circulating miRNAs. Obviously, application of direct amplification of circulating miRNAs

from plasma without RNA extraction will be a novel approach for the detection and quantification of circulating miRNAs so as to predict the cancer in near future.

Expression of diversified miRNAs in multifarious human cancers is really wonderful. In the last 25 years, technological innovations based miRNA profiling techniques have clearly revolutionized the elucidation of miRNA expression pattern in different pathophysiological conditions of the body, The complex relationships between miRNAs and their functional pathways, their role in cell-cell communication, stability in cancer tissues and circulating body-fluids as well as their exogenicity in therapeutic use are yet to be conceptualised. Biogenesis, differential pattern of expression, and nature of action turn miRNA into master molecule in cancer biology. MicroRNAs are really small, but most powerful biomolecules and have big responses which extend from cancer prognosis to diagnosis to therapeutics in near future.

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