Micrornas as Double Edged Sword in Cancer

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ABSTRACT

Cancer is the leading causes of death world wide. Basically it can be defined as the disease of the cell. One among the mechanism of transfer of a normal cell to cancerous is the alteration in the genetic material DNA. Treatment for cancer remains as a biggest challenge. Here comes the importance of miRNAs. They are endogenous RNA which regulates a wide range of cellular processes such as proliferation, differentiation, development and apoptosis by suppressing the expression of target mRNA thus playing a central role in various human diseases including cancer. Hence advancement in miRNA research is necessary to develop it as a powerful therapeutic tool in cancer. Oncomirs are miRNAs acts as double edged sword in cancer because up-regulation and down-regulation of miRNAs are observed in cancerous cells and hence acts as oncogenes and tumor suppressors respectively. miRNAs can act as potential biomarkers. Studies shows that the change in level of miRNA are directly associated with cancer. Hence till-date reviewing as onco-miRs is necessary which further the researcher to develop it as a specific and potential target in cancer treatment. miRNAs are promising therapeutic tools for cancer because in humans, 50% of miRNA genes were localized in cancer-associated genomic regions which include minimal regions of amplification, loss of heterozygosity, fragile sites and common breakpoint regions. miRNA are found to be up-regulated and down-regulated in almost all cancer cells. Hence, in this article an attempt is made to review the evidence of microRNAs in cancer as both oncogenes and tumor suppressors.

Keywords: MicroRNA, Double Edged Sword Tumor Suppressors, Onco-miRs, Gene Regulation

1. INTRODUCTION

MicroRNAs are small ~22 nucleotides (nt) long, non protein coding, single stranded RNAs found in both plants and animals (Bartel, 2004). Lee et al. (1993) in the Victor Ambros lab first discovered miRNA, lin-4 in Caenorhabditis elegans through a genetic screen for defects in the temporal control of post-embryonic development. The term microRNA was coined (Ruvkun, 2001). Unlike siRNA, they are found endogenous (Bartel, 2004; Ambros, 2001; Carrington and Ambros, 2003). Many miRNAs are found to be highly conserved molecules (Pasquinelli et al., 2000). The complete mature miRNA sequence of let-7, isolated primarily in Caenorhabditis elegans, has been evolutionarily conserved from worms to humans (Lee and Ambros, 2001). Currently, thousands of miRNAs have been identified in nematodes, amphibians, fishes, plants, mammals and viruses (Zhang et al., 2006a) using different approaches including experimental methods, computational approaches, EST and Genomic Survey Sequence analysis (Lee and Ambros, 2001; Brown and Sansseau, 2005; Zhang et al., 2005; 2006b). Out of hundreds of miRNAs that have recently been identified, only about 200-300 miRNAs have been currently identified in humans (Griffiths-Jones, 2004; Griffiths-Jones et al., 2006). Studies prove that miRNAs could also cause gene silencing (Lee et al., 1993; Pasquinelli et al., 2000;
Wightman et al., 1993; Olsen and Ambros, 1999; Reinhart et al., 2000). Recent evidence indicates that miRNAs exhibit important regulatory roles in development, cell proliferation, cell survival and apoptosis and thus play a central role in gene regulation in health and disease (Bentwich et al., 2005; He and Hannon, 2004; Meltzer, 2005). In this review, we briefly gene regulation of miRNA, its association with cancer, furthermore with instances to prove it as tumor suppressors and oncogenes.

1.1. miRNA Gene Regulation

In humans, miRNAs target more than 30% of protein coding genes (Berezikov et al., 2005; Lewis et al., 2005) and the total number of miRNAs by computational analysis indicates there may be more than 1% of the total protein coding genes (Lai et al., 2003; Lim et al., 2003a; 2003b). MicroRNA biogenesis and mechanism of gene repression are similar to those of exogenous small interfering RNAs (siRNAs) (Izquierdo, 2005). The genes encoding miRNAs are much longer than the processed mature miRNA molecule. MicroRNAs negatively regulate the target gene expression in a variety of ways including translational repression, mRNA cleavage and deadenylation. MicroRNAs can direct RISC to down-regulate gene expression by binding with perfect or nearly perfect complementarity to protein coding mRNA sequences. Most animal miRNAs are thought to use a gene regulation mechanism that does not involve the cleavage of their mRNA targets (Filipowicz et al., 2005). RISC is a ribonucleoprotein complex containing members of the Argonaute (Ago) family of proteins. Argonaute is also partially responsible for selection of the guide strand (incorporated strand) on the basis of the stability of the 5’ end and destruction of the passenger strand. The strand with lower stability base pairing of the 2-4 nt at the 5’ end of the duplex preferentially associates with RISC and thus becomes the active miRNA (Schwarz et al., 2003). MiRNA genes can be located in the introns and/or exons of protein-coding genes or in the intergenic regions between protein-coding genes. They can form polycistronic clusters or exist individually (Bartel, 2004; Lagos-Quintana et al., 2001; Kim and Nam, 2006). A single miRNA could regulate multiple target genes, while a single gene could be targeted by multiple miRNA (Wu et al., 2006). Location of miRNA near protein coding genes and its ability to regulate genes proves its importance in medicine.

1.2. miRNAs and Cancer

Cancer is a complex genetic disease in which oncogene amplification and/or tumor suppressor gene mutation leads to step-wise deregulation of cell proliferation and apoptosis (Wu et al., 2006). A number of studies reported that specific microRNA signature had been found in each cancer tissue and microRNA-based cancer classification is a very effective and potential tool (Lu et al., 2005). The involvement of miRNAs in cancers was confirmed through the observation that miRNAs are frequently located in cancer-associated genomic regions, which include minimal regions of amplification, loss of heterozygosity, fragile sites and common breakpoint regions in or near oncogenes or tumor suppressor genes (Calin et al., 2004a). The first report linking miRNAs and cancer involves CLL (B cell lymphocytic leukemia) (Calin et al., 2002). miRNAs show globally lower expression in cancer tissues than in normal tissues (Lu et al., 2005). Abnormalities in miRNA expression have been implicated in several forms of solid tumors such as cervical (Lee et al., 2008), breast (Lorio et al., 2005), colorectal (Cummins et al., 2006), lung (Hayashita et al., 2005) and also in at least two forms of leukemia (Calin et al., 2004a; 2004b). Axissar et al. (2009) used quantitative RT-PCR to study the expression of miR-375 in Head and Neck Squamous Cell Carcinomas (HNSCCs), found higher expression of this miRNA in tumors of pharyngeal and laryngeal origin suggesting that alterations in miRNA expression are related to cancers and are useful biomarkers in cancers. This instance shows the role of miRNA in cancer and as potent biomarker.

1.3. miRNAs as Tumor Suppressor

A variety of miRNAs have been identified that appear to have tumor suppressor functions. A recent study has shown that there is a global down-regulation of miRNA expression in various tumor tissues (Lu et al., 2005). B Cell Lymphocytic Leukemia (CLL) is characterized by the deletion of miR-15a and miR-16-1, two clustered miRNAs, within the 13q14.3 locus (Calin et al., 2002). Deletions at this region also occur in approximately 50% of mantle cell lymphoma, in 16-40% of multiple myeloma and in 60% of prostate cancers, suggesting the location of one or more tumor suppressor genes at this locus (Dong et al., 2001). Northern analysis suggested that both miRNAs were down-regulated in the majority of cases (approximately 70%). A predicted target of these miRNAs is B cell lymphoma 2 (Bcl2), an anti-apoptotic
protein. The down-regulation of miR-15 and miR-16 leads to an increase in Bcl2 expression (Cimmino et al., 2005). miR-15a and miR-16-1 were also expressed at lower levels in pituitary adenomas as compared to normal pituitary tissue and their expression inversely correlated with tumor size (Bottoni et al., 2005).

Let-7 miRNAs are considered as classical tumor suppressors due to their frequent down-regulation in cancers like lung or colon (Lu et al., 2005; Volinia et al., 2006). Ras oncoproteins were the first target described to be regulated by the let-7 miRNA family. In both C. elegans and human lung cancer cell lines let-7 negatively regulated RAS (Johnson et al., 2005) and it was not expressed in human lung cancer tissues (Johnson et al., 2005; Takamizawa et al., 2004). Furthermore, overexpression of let-7 in A549 lung adenocarcinoma cell line inhibited lung cancer cell growth (Takamizawa et al., 2004).

Recent studies reported that another target of let-7 miRNA family is High mobility group a2 (Hmg2a) protein, oncogenic in a variety of tumors, including benign mesenchymal tumors and lung cancers. Chromosomal translocations disrupt the repression of Hmg2a by let-7 miRNA which promotes anchorage-independent growth, a characteristic of oncogenic transformation (Lee and Dutta, 2007; Mayt et al., 2007). In lung cancer cell line restoration of the steady state levels of let-7 inhibited cell replication. Studies in human colon cancer tumors and cell lines show that in addition to Ras, c-Myc might also be a target of let-7 as its expression reduces levels of RAS and c-MYC proteins (Akao et al., 2006), miR-143 and miR-145 has been found to be down-regulated in colorectal cancers (Slaby et al., 2007), B-cell lymphomas (Akao et al., 2007) and in cervical cancers (Lui et al., 2007; Martinez et al., 2008). A recent report showed that TCL1, an oncogene that is overexpressed in CLL cells (Herling et al., 2006) and Mcl-1, an anti-apoptotic Bel-2 family member (Mott et al., 2007) are targets of miR-29 genes (Pekarsky et al., 2006).

Ciafre et al. (2005) identified a group of miRNAs: miR-128, miR-181a, miR-181b and miR-181c were down-regulated in glioblastoma (Ciafre et al., 2005). In primary neuroblastoma tumors, miR-34a on chromosome 1p36.23 was generally expressed at lower levels and it directly targeted the mRNA encoding E2F3 and significantly reduced E2F3 protein levels. This result suggested that miR-34a acted as a tumor suppressor of neuroblastoma tumorigenesis (Welch et al., 2007). MiR-34a was frequently absent in pancreatic cancer cells and its responsive genes were highly enriched for those that regulated cell-cycle progression, apoptosis, DNA repair and angiogenesis (Chang et al., 2007). Slack’s research group demonstrates that let-7 miRNA inhibits the growth of lung cancer cells in culture and in lung tumors in mice. They also showed that let-7 can be applied as an intranasal drug to reduce tumor formation in a RAS mouse model lung cancer (Esquela-Kerscher et al., 2008).

Bhattacharya et al. (2009) identified two miRNAs, miR-15a and miR-16, that are underexpressed in ovarian cell lines and in primary ovarian tissues. Oncogenic activation of Bmi-1 is found in a wide variety of epithelial malignancies including ovarian cancer. Bmi-1 protein levels are down-regulated in response to miR-15a or miR-16 expression and lead to significant reduction in ovarian cancer cell proliferation and clonal growth, suggesting the development of therapeutic strategies by restoring miR-15a and miR-16 expression in ovarian cancer and in other cancers (Bhattacharya et al., 2009).

1.4. miRNA as oncogenes

He and colleagues found the over expression of the miR-17-92 polycistron at 13q31.3 in B-cell lymphomas (He et al., 2005). It is also found to be over expressed in several other cancers such as solid cancers (Volinia et al., 2006), lung cancer (Hayashita et al., 2005) and malignant lymphoma cell lines (Tagawa and Seto, 2005) proving it as potential oncogenes. Recent studies in mouse B-cell lymphoma model reveals miR-19 is a key oncogenic component of mir-17-92 cluster (Olive et al., 2009). In breast tumors miR-21 was found to be over expressed when compared to normal breast tissues (Iorio et al., 2005; Si et al., 2007). Zhu et al. (2007) identified down-regulation of tumor suppressor, tropomyosin 1 in breast cancer by miR-21 could result in tumor growth supporting the notion that tropomyosin 1 as a potential miR-21 target. It was found to be over expressed in head and neck cancer cell lines (Tran et al., 2007), brain tumor and glioblastoma (Chan et al., 2005) proving it as an oncogene. The glioblastoma tissues and glioblastoma cell lines analysis shows strong upregulation of miR-221 (Ciafre et al., 2005).

In cervical cancer tissues, increased expression of miR-15b, miR-16, miR-146a, miR-155 and miR-223 has been observed. Cimmino et al. (2005) reported that miR-15 and miR-16 regulate apoptosis by targeting BCL2. miR-155 was found over expressed in lung cancer (Yanaihara et al., 2006), lymphoblastic leukemia/high-grade lymphoma (Calin et al., 2005), B-cell
lymphomas, Hodgkin’s lymphomas, Burkitt lymphomas and in human breast cancer cells suggesting that it may act as oncogene (Iorio et al., 2005; Metzler et al., 2004; Eis et al., 2005; Kluiver et al., 2005).

Studies proved that miRNA expression can be regulated by DNA methylation and it has been suggested that altered miRNA gene methylation might contribute to human tumorigenesis. Let-7a-3 was found to be methylated by the DNA methyltransferases DNMT1 and DNMT3B. The gene was heavily methylated in normal human tissues but hypomethylated in some lung adenocarcinomas. Brueckner et al. (2007) identified let-7a-3 as epigenetically regulated miRNA gene with oncogeneic function and suggest that aberrant miRNA gene methylation might contribute to the human cancer epigenome. Analysis of human breast tumors by Wang et al. (2009) revealed that miR-27b expression increases during cancer progression, paralleling a decrease in Suppressor of Tumorigenicity 14 (ST14) expression. The 3'-untranslated region of ST14 contains a regulatory element for miR-27b and luciferase experiments indicate that antisense miR-27b enhances ST14 expression in cancer cells which reduces cell proliferation as well as cell migration and invasion. Knockdown or over expression of a specific miRNA allows studying the specific roles of the miRNA in cancer development.

2. CONCLUSION

Oncogenic micro RNAs or Oncomirs are miRNAs with a role in cancer. The first functional evidence of a miRNA, or any non-coding RNA, acting as a mammalian oncogene is about mir-17-92 from studies of Hammond (2006) in B-cell lymphoma. For this reason they refer the host transcript of mir-17-92 as OncomiR-1 (Hammond, 2006). The above discussions clearly reveal that miR-27b and luciferase experiments indicate that antisense miR-27b enhances ST14 expression in cancer cells which reduces cell proliferation as well as cell migration and invasion. Knockdown or over expression of a specific miRNA allows studying the specific roles of the miRNA in cancer development.

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