MERIT RESEARCH JOURNALS
www.meritresearchjournals.org
Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-3238) Vol. 3(1) pp. xxx-xxx, January, 2015
Available online http://www.meritresearchjournals.org/mms/index.htm

Short Communication

Role of MicroRNA in Cancer Diagnosis and Therapeutics: A Mini Review

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Abstract

MicroRNAs (miRNA) - a novel class of small noncoding RNAs genes. Their final product is a twenty two nucleotides functional molecule of RNA. These small non-coding RNAs silence and target several genes through varied signalling pathways that include important physiological networks. MiRNAs regulates post-transcriptional expression of genes. The miRNA was discovered as small temporal RNA (stRNA) regulating development transition in *Caenorhabditis elegans*. The miRNAs have an enthusiastic part in neoplastic transformations either by elevating expression of oncogenes or reducing tumours suppressor genes and oncogene. Although miRNAs are key gene regulators, yet experimental and computational approaches are still scanty. Complete understanding of this prime regulating transcript class is still in need of exuberated research. The current article is reviewing miRNA, its discovery, role of miRNAs in suppression of tumours and oncogenes and role of miRNA in diagnosing cancer and its therapy.

Keywords: Cancer, Discovery, Diagnosis, MicroRNA, Oncogenes, Suppression, Therapy Tumours.

INTRODUCTION

Discovery of MicroRNA (miRNA)

MicroRNA (miRNA) was discovered in 1993 (Mada et al., 2013). Primarily it was known as a small non-coding, lin-4, RNA in *Caenorhabditis elegans* (Pasquinelli and Ruvkun, 2002). It was observed as expression modifier of lin-14 protein (Lee et al., 1993; Wightman et al., 1993). After some years, l3t-7, a second miRNA was discovered in *Caenorhabditis elegans* (Reinhart et al., 2000). These discoveries paved the way for further discovery of new MicroRNAs. Now there is a huge class of non-coding small RNAs having a wide range of biological functions, such as tumourigenesis, cell death and proliferation, and haematopoiesis (Bartel and Chen, 2004; Kim et al., 2009). These MicroRNAs are also variable as for as length and structure is concern.

MicroRNA

MicroRNAs (miRNAs) are small, endogenous, noncoding RNAs, usually between 18 and 25 nucleotides in length, involved in the regulation of cellular and developmental processes through post-transcriptional gene suppression (Pasquinelli and Ruvkun, 2002; He and Hanon, 2004; Sun and Lai, 2013). These are expressed either as single transcription unit or as polycistronic transcripts from miRNA clusters, encoded within intronic or intergenic regions of the genome (Kloosterman and Plasterk, 2006; Lee et al., 2002). Primary or pri-miRNAs are formed by polymerase II that drives transcription of miRNAs as inverted repeats embedded in long primary transcripts, which spontaneously fold to form imperfect long hairpins (Ambros, 2007; Tian, 2004; Kim et al., 2009). It is then processed into shorter hairpin precursor miRNAs, or pre-miRNAs, in the nucleus by RNase III enzyme complex of DROSHA (RNASEN)/DGCR8 (Moazed, 2009). Pre miRNAs are transferred into cytoplasm by a trans-nuclear membrane protein called exportin 5 (XPO5) (Tian, 2004; Kim et al., 2009). In cytoplasm, the RNase III enzyme DICER1 cut the pre-miRNA to form a double-stranded miRNA duplex comprising a mature miRNA (guide

strand) and a partially complementary passenger, or ‘‘star’’ (*), strand (Han, 2010; Kohler and Hurt, 2007). The fully matured miRNA associates with argonaute proteins in the RNA-induced silencing complex (RISC) to direct translational repression by binding to the regions of complementarily in 3′ untranslated regions of target mRNAs (Iwasaki et al., 2013; Macfarlane and Murphy, 2010).

RISC loading has been shown to be largely asymmetric, with only a single strand of miRNA duplex being incorporated to direct gene silencing (Tomari and Zamore, 2005). However, some miRNA duplexes encode mature miRNAs on both strands, and recent evidence suggests that strand based in miRNA expression may be influenced by tissue-specific processing factors (Ambors and Chen, 2007). The altered expression may be due to a variety of mechanisms including transcriptional regulation, amplification, deletion, mutation, and epigenetic silencing (Pillai, 2005). Although miRNA signatures were established in tumor cells (Thomson et al., 2011; Siomi and Siomi, 2010), recent studies revealed that the potential capabilities of miRNAs as blood-based biomarkers for cancer and other diseases (Iorio and Croce, 2012).

Approximately 98% of RNAs in mammalian cells do not code for proteins. The epigenetic factors are associated with hearing loss (Volinia et al., 2006), elevating the possibility that noncoding RNAs, such as miRNAs, might also involve in inner ear development and hearing loss etc. (Rahman et al., 2014).

Suppression of Tumour and Oncogene by MiRNAs

MicroRNAs is a novel and vital class of tumour and oncogene suppressing genes (Tazawa et al., 2007). MicroRNAs involvement in tumours are centred on distinctive expression in neoplastic tissue in a tumorous specific manner as compare to normal tissue (Tavazoie et al., 2008) and in primary tumours when compare to metastatic tissues (Volinia et al., 2006). MiRNAs are supposed to work as oncogenes, when there expression is elevated in tumours. In this condition these are known as oncomirs, hindering tumour supressing genes negatively. This is accompanied by cell differentiation arrest or apoptosis, hence promoting development of tumours. A candidate oncogenic miRNA by the name of MiR-184 plays an important part in anti-apoptosis and propagation of tongues SCC cells (Wong et al., 2008). MiR-16-1 and miR-15a are classical examples of tumour supressing gene MicroRNA.

A cluster at the stage of chromosome 13q14.3, a region commonly deleted in chronic lymphocytic leukemia (Bullrich et al., 2001), miR-15a and -16 exhibit expression levels inversely associated to the BCL2 (Rani et al., 2014). Some miRNAs showed reduced exp-ression in cancer cells, therefore considered as tumours suppressing genes. Tumour suppressor miRNAs prevent tumour progression by oncogene inhibition negatively and inhibiting genes controlling apoptosis or cell differentiation (Ullah et al., 2014). One of the founding members of MicroRNA family, miRNA let-7 is greatly preserved (Lotterman et al., 2008). This miRNA is usually deleted in cancers and is constrained to a chromosome region.

MicroRNAs’ Role in Cancer Diagnosis and Therapy

The MicroRNAs capability of regulating apoptosis and cell growth is an aspect of its function in pathogenesis of cancer, resulted from growth dysregulation of cells’ apoptosis. Sequentially miss-expression or over expression of specific miRNAs has to be identified for recognizing miRNAs’ role in pathogenesis of cancer and to show initiation and advancement different forms of malignancies. miRNAs can be categorized based on human cancer by identifying miRNAs, that are unpredictably expressed among tumour and normal tissues. Furthermore this can be helpful in finding miRNAs role in diagnosing cancer as a biomarker (Iorio et al., 2005). Abnormal expression of miRNA in oral squamous cell carcinoma is a key marker for diagnosing and detecting early cancer as well as predicting prognostics (Rani et al., 2014). MicroRNAs are also known to have key role in various cellular processes like receptor drive pathways, proliferation and apoptosis.

MicroRNAs’ Delivery

Delivery of miRNAs into target tissues, their efficacy and solidarity in those tissues still remains to be a main problem in RNA-based direct therapies. Giving MicroRNA-34a in complex with atelocollagen subcutaneously inhibits progression of cancer and was proved as a powerful system, having capability of in vivo delivering of small molecules (interfering RNAs) into tumour. MiR-34 is known as one of the best tumour suppressor miRNAs downstream p53 and promotes genes taking part in cell cycle arrest, apoptosis and cellular senescence (Bader et al., 2010; Bae et al., 2012; Ullah et al., 2014).

CONCLUSION

In this revolutionized era when biomedical sciences have got a strengthened position, MicroRNAs are recognized as potential regulators (post-transcriptionally) of gene expression. This is done by simultaneous inflection of several target genes. A lot of work done on miRNA, revealed enormous information regarding miRNA-mediated regulation of genes as well as their character in

diseases. Association of miRNAs dysregulation with initiation of cancer and its progression, which may be due to apoptosis inflection, is one the most widely aspect of research under its way. This emergence of involving miRNAs dysregulation with cancer is playing an important factor in diagnosis, therapy and prognosis of cancer.

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