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MicroRNA in human cancer and chronic inflammatory diseases

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1. ABSTRACT

MicroRNAs (miRNAs) are the non-coding RNAs that act as post-translational regulators to their complimentary messenger RNAs (mRNA). Due to their specific gene silencing property, miRNAs have been implicated in a number of cellular and developmental processes. Also, it has been proposed that a particular set of miRNA spectrum is expressed only in a particular type of tissue. Many interesting findings related to the differential expression of miRNAs in various human diseases including several types of cancers, neurodegenerative diseasesw and metabolic diseases have been reported. Deregulation of miRNA expression in different types of human diseases and the roles various miRNAs play as tumour suppressors as well as oncogenes, suggest their contribution to cancer and/or in other disease development. These findings have possible implications in the development of diagnostics and/or therapeutics in human malignancies. In this review, we discuss various miRNAs that are differentially expressed in human chronic inflammatory diseases, neurodegenerative diseases, cancer and the further prospective development of miRNA based diagnostics and therapeutics.

2. INTRODUCTION

MicroRNAs (miRNAs) are small 18-24 nucleotide long oligomers, which were initially thought to be a part of junk DNA. Lee and co-workers (1) were the first to report a gene, *lin-4* responsible for post embryonic development in *Caenorhabditis. elegans*. This gene product, which is a 22 nucleotide RNA proved to be responsible for degradation of lin-4 mRNA, by interacting with its 3'-untranslated region (UTR). Later on, discovery of let7, another small RNA oligonucleotide, responsible for developmental timing in *C. elegans* and its sequence conservation among various organisms led to a notion that small RNA molecules can control gene expression (2). A decade later, more than 500 miRNAs were identified (3),with distinct roles in cell proliferation, apoptosis and organogenesis (4, 5). With their natural role in cell proliferation, imbalances in miRNA expressions are found to be significant in the development and progression of cancers and other immunological disorders (6, 7). On the basis of findings that specific cell type has specific miRNA signatures (8, 9), which in turn might play key roles in disease development; one can expect the use of miRNA in diagnosis and prevention of various human diseases. As a

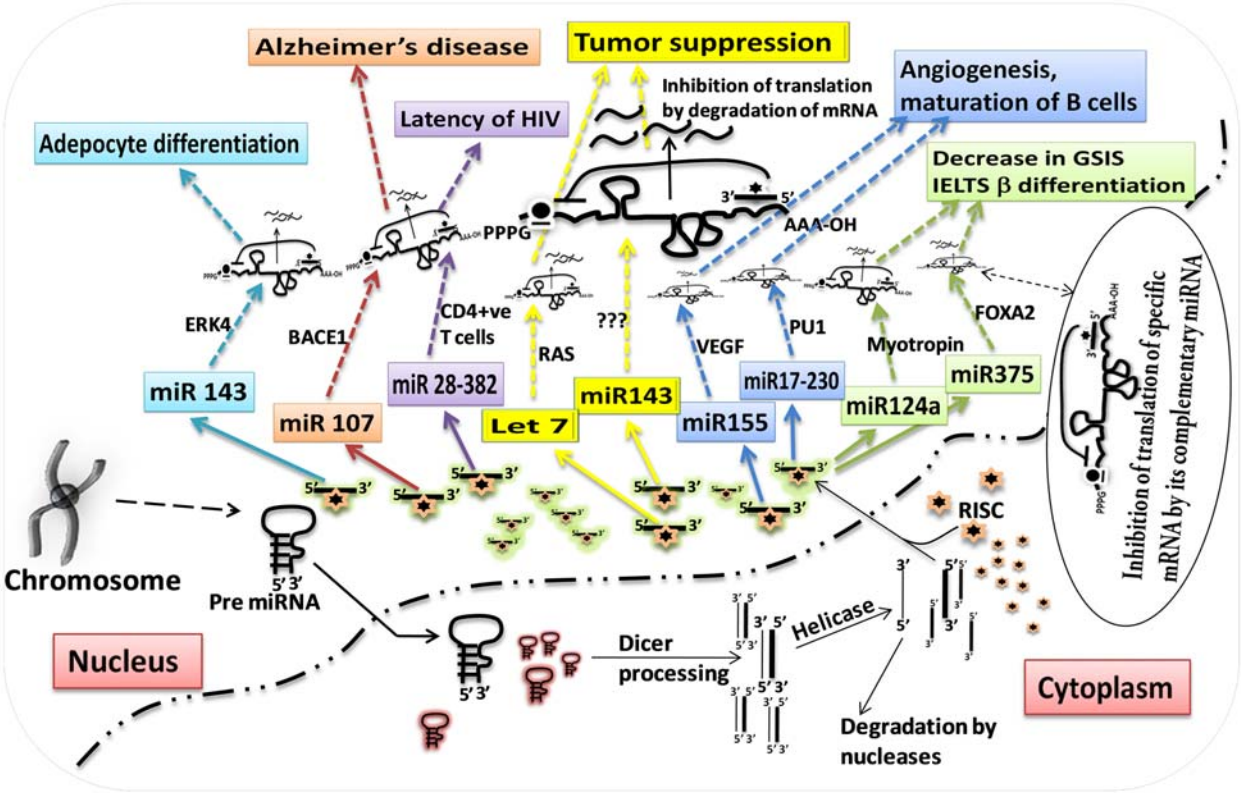

Figure 1. RNA polymerase II transcribes large pri miRNA from their corresponding genes. RNA III enzyme Drosha/Pasha, then acts on the pre miRNA to make them pre miRNAs. These pre miRNAs then exported from the nucleus in a GTP dependent fashion by exportin5 and become mature miRNA, in the cytoplasm after further processing by another RNAse III enzyme, Dicer. The released double stranded ~22 nt duplexes incorporated in to RNA induced silencing (RISC) complex. The complex now can regulate corresponding mRNA, which is complimentary to the 5' end (miRNA seed) of the miRISC complex.

small oligo miRNA is more stable *in vitro,* compared to mRNA, indicating the potential of using miRNA in diagnostic markers (10). A recent work comprising miRNA expression profiles in estrogen receptor (ER) + ve and ER-ve breast cancer samples based on qRT-PCR (11) is one such example. Also, anti-miR antagomirs can be used as therapeutic targets (12, 13). There are 1000 or more reviews on miRNA biology and the roles of miRNA in disease development have also been reviewed recently (14-16). These articles mostly summarize the computationally identified targets. In this review, we discuss specifically identified targets, in addition to computational targets of miRNA expressed in human cancer, chronic inflammatory and neurodegenerative diseases.

3. MIRNA BIO-GENESIS AND FUNCTION

The majority of miRNAs originate after a series of processes from their precursor molecules termed pri-miRNAs which are generated by transcription of corresponding gene by RNA polymerase II. Pri-miRNAs are stem loop structures capped at 5' end, polyadenylated and are usually spliced. The RNase III enzyme Drosha then cleaves these oligonucleotides into further small pre-miRNA, with the use of its cofactors Digeorge syndrome critical region gene 8 (DGRC8) and RNA helicase (Figure 1). After this step, they are exported from the nucleus to the cytoplasm by exportin-5 in a Ran guanosine phosphate dependent manner (17). These pre-miRNAs are further processed in the cytoplasm by another RNAse III enzyme called Dicer, along with its cofactor, trans activation-response RNA binding protein (TRBP), to produce ~22 nt miRNA duplexes. This duplex then binds to the RNA induced silencing complex (RISC). The RISC-miRNA complex then binds to the corresponding mRNA and represses its translation by blocking translation initiation or by inducing endonucleolytic cleavage of mRNA. Conversely, miRNAs can enhance translation as suggested recently by Tili *et al* (18). It has been observed that miR-155's over expression results in enhanced translation of Tumor Necrosis Factor α (TNF-α), most probably by enhancing the stability of its transcript, and mice over expressing miR-155 in B cell lineage (Eμ-miR-155,) produce more TNF-α when challenged with LPS (18). Further research in detailed, in a realistic approach is needed to confirm the role of miRNAs in enhancing gene expression and translation of proteins. More recently, an increase in number of reports and the new discoveries of miRNAs indicate their potential roles in regulation of key genes involved in metabolic pathways and cellular processes such as cell proliferation, apoptosis, insulin secretion, haematopoiesis and adipocyte differentiation. In

Table 1. Different miRNAs involved in various human diseases as listed. Several miRNAs are found to be common in regulating different diseases, via different mechanisms

Tumor suppression	miR15a (6), miR16-1 (23), Let7 (25), miR-145 (26), miR23 (74)
Tumor progression	miR155 (77), miR21 (31), miR371&373 (30)
Tumor Angiogenesis	miR126 (75, 76), miR-296 (47)
Diabetes and metabolic diseases (Ref)	miR375 (45), miR124a (48), miR143 (53), miR21 (60), miR155 (88)
NDDS (Ref)	miR133b (58), miR107 (59), miR128a (61), miR29a/b-1 (60), miR-19, miR-101, miR-130 (64), miR146a (61), miR-342-3p, miR-320, let-7b, miR-328, miR-128, miR-139-5p, miR-146a (65)
Inflammation and vascular diseases (Ref)	miR150 (84), miR223 (87), miR155 (77-80), miR21 (88), miR126 (74-76)
Viral infection (Ref)	miR146a (93, 94, 99), miR155 (95), miR34a (101), miR122 (102), miR Tar (97), miR-181a, miR-181b, miR-200b (93),

this regard, they have been associated with the occurrence and progression of most prevalent human diseases such as cancer, heart diseases and neurodegenerative diseases (19-21).

3.1. miRNA in human cancer

The process of cancer development involves sequence of highly ordered mechanisms such as carcinogenesis and metastasis. Mutated cells, which overcome the apoptosis process, develop into a dormant tumor, the later becomes life threatening after the formation of angiogenic networks and metastasis (22). As a whole, cancer is an abnormality, formed from normal tissue. Since miRNA, have shown to have tissue specific signatures, one would wonder about their roles in the development of cancer. The first evidence for the link between miRNA and cancer comes from the study that miR15 and miR16 are located at chromosome 13q14, a region deleted in more than half of B cell chronic lymphocytic leukemias (B-CLL) (6). Detailed deletion and expression analysis showed that miR15 and miR16 were located within a 30-kb region of loss in CLL, and that both genes were deleted or down-regulated in the majority (≈68%) of CLL cases (23). The expression of miR15a and miR16-1.has been inversely correlated to Bcl2 expression in CLL and that both microRNAs negatively regulate Bcl2 at a posttranscriptional level showing the tumor suppressor functions of miRNA. The data presented in this study is of considerable therapeutic significance, since miR-15 and miR-16 have natural antisense Bcl2 interactions that could be employed for therapy in tumors over expressing Bcl2. An important group of miRNAs, the let-7 family (found to regulate RAS and/or MYC oncogene expressions at the translational level), often down-regulated in human colon tumors owing to its growth repression functions (24, 25). Recent evidence suggests that miR143 and miR145 are consistently down-regulated in colorectal tumors (26). Also it has been shown that down-regulation of these miRNAs is a common occurrence in breast carcinomas and breast tumor cell lines (27). On the flip side, miRNAs acting as oncogenes have also been identified, owing to speculations about their role in tumourigenesis. B cell integration cluster (BIC) or miR155 was shown to accelerate MYC mediated lymphoma cells in a chicken model (28). Another cluster of 6 miRNAs has implications in the development of large B cell lymphoma and these 66 miRNAs can act as potential oncogenes (29). miR372 and miR373 were found to block RAS induced cellular senescence and potentiate RAS mediated cellular transformation (30).

Cancer cells have been proved to have different miRNA expression profiles, as compared to normal cells, suggesting that miRNA expression could be used for diagnosis of cancer. miR-21 expression was found to be increased in glioblastoma, as compared to normal brain autopsies (31). Takamizawa *et al.* (32) have shown significant reduction in let7 miRNA in lung cancers by Northern blotting. When compared with let7 miRNA basal expression in normal lung tissue, as frequent as 43.8% of all lung cancer tissues showed > 80% reduction in let7 miRNA levels., These reports suggest that over expression of miR 21 (~100 fold increase of miR21, as indicated by Northern blotting and membrane array in the study) and/or under expression of let7 miRNA are more commonly observed in cancer tissues, thus can be used as potential biomarkers for glioblastoma and lung cancer respectively (32). Differential expression profiling of breast cancer and normal breast tissues revealed discrepancy in the expression of 29 miRNAs. . Both miR21 and 155 were found to be up regulated, where as miR-10b, miR125b and miR-145 were down-regulated, suggesting that these miRNAs can be potentially used as diagnostic markers (33). In a study on 17 poorly differentiated tumor samples, when both miRNA and mRNA microarrays were used in parallel, miRNA microarray was found to be more sensitive for classification of 12 of 17 tumor types, where as mRNA microarray could correctly classified only one sample (34), indicating the potential uses of miRNA over mRNA in future diagnostics. Recently, when miRNA expression profiles of 144 lung cancer and control tissue samples were determined by using 352 probes for miRNA, 43 miRNA expression profiles consistently differed from normal controls (35). Out of these, 8 miRNAs viz. miRs-17-3p,-21,-93, -106a, -145, -155, let-7a-2 and let-7b were found to be survival prognosticators (Table 1).

Another study confirms that miRNA expression in peripheral blood could be used as a substitute of miRNA expression in the tumor biopsy. Tumor-derived exosomes are small membrane vesicles of endocytic origin released by the tumor and found in the peripheral circulation. There are reports which have been shown that exosomes could be an important resource of cell-free miRNA in serum or plasma (36-38). More recently, in relation to evaluation of circulating levels of tumor exosomes, exosomal small RNAs in patients with and without lung adenocarcinoma, an increase in protein concentration in circulating exosomes has been reported (39) The authors tested levels of 12 miRNAs that have been reportedly modulated in lung cancers including miR21 and 155. In all 4 lung adenocarcinoma cases, there was no significant difference in miRNA levels of paired tumor and plasma samples, and there was similarity between circulating miRNAs of tumor-derived exosomes and tumor miRNAs (39). In

another study (40), based on detection of serum miRNA loads for breast cancer diagnosis, analysis of serum samples from 21 subjects, women with progesterone positive breast cancer showed predominance in miR 155, compared to controls, while other miRNAs, detected in this study including miR16 and 145 doesn't show any such variation. This approach therefore, can lead to the development of a noninvasive, blood-based detection test for breast cancer, Measuring the expression of specific circulating miRNAs in cancer patients can be a good substitute to tumor tissue specific miRNA expression, thereby initiates a new paradigm that will be useful not only for early diagnosis but also for prognostic and therapeutic decisions (41). Taken together, certain miRNAs can be used as diagnostic markers in cancer detection.

3.2. miRNA in diabetes and metabolic diseases

Diabetes is currently the most prevalent metabolic disorder affecting over 150 million people all over the world (42). It is a chronic disorder of carbohydrate metabolism, usually occurring in genetically predisposed individuals, characterized by inadequate production or utilization of insulin and resulting in excessive amounts of glucose in the blood and urine, excessive thirst, weight loss, and in some cases progressive destruction of small blood vessels leading to complications such as infections and gangrene of the limbs or blindness. Although many sub classes with same symptoms have been identified and classified, Diabetes mellitus (DM) is the most predominant disease. DM is further classified into two types, type I and type II. Type I and/or insulin dependent DM (IDDM), is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to a deficiency of insulin. The majority of type I diabetes is of the immune-mediated variety, where beta cell loss is a T-cell mediated autoimmune attack (43). Type II or non insulin dependent DM is due to insulin resistance or reduced insulin sensitivity, combined with relatively reduced insulin secretion which in some cases becomes absolute (44). Studies regarding miRNA profiles in DM and obesity, have implicated miRNAs in these diseases. A small spectrum of miRNAs including miR-375, miR124a and miR-9 has been proven to have implications in diabetes. Poy and co workers (45) have cloned miR375, from pancreatic islets and observed that over-expression of miR-375 suppressed glucose-induced insulin secretion (GSIS). Conversely, inhibition of endogenous miR-375 expression is able to enhance insulin secretion. This mechanism has been proven to be independent of glucose metabolism and/or calcium signaling but was found to correlate with insulin exocytosis. Further studies indicated that, myotropin, a putative target of miR375, was responsible for GSIS. Also, knockdown of miR-375 in zebra fish embryos has shown its potential role in pancreatic islet development (46). Screening of the pancreatic β-cell line MIN6 to identify miRNAs with altered abundance in response to changes in glucose concentrations has resulted in identification of 61 glucose-regulated miRNAs from a detectable total of 108 miRNAs. Some of these miRNAs, including miR-296, miR-484, and miR-690 were significantly down-regulated by high glucose treatment. Many of the identified miRNAs, including miR-124a, miR-107, and miR-30d were up-regulated in the presence of high glucose, out of which miR30d increased insulin gene expression, while inhibition of miR-30d abolished glucose-stimulated insulin gene transcription by GSIS. These results suggest that the direct and/or indirect regulation of repressor genes is involved in insulin secretion (47).

An interesting study on miRNA expression profiling at two key stages of mouse embryonic pancreas development, e14.5 and e18.5 reported that MiR124a2 isoform was found to be differentially expressed using embryonic stage e18.5 (48). Using pro- and anti-miR technology, FOXA2 mRNA was found to be a putative target of miR124a. FOXA2 gene appears to play a pivotal role in key β-cell functions and physiology (48, 49), Also, cyclic AMP response element binding protein (CREB) mRNA was found to be regulated by miR-124a as well. The data thus suggested that Creb-1 may be a transcription factor regulating Foxa2 expression that, in part, might explain the observed up-regulation of the gene when cells are treated with anti-miR-124a2.FOXA2 is knownd to control pancreatic duodenum homeobox-1 (Pdx1), which in turn controls β cell differentiation and insulin gene expression (48-50). Also K_{ATP} channel subunits, SUR1 ((sulfonylurea receptor 1) and KIR6.2 (inward rectifier K^+ channel member 6.2), which are critical for insulin release and FOXA2 dependent (49), were found to be regulated by miR124a2. Further downstream effectors of FOXA2 include Rab 27a, which is involved in GSIS and other proteins involved in exocytosis including SNAP 25, RAB3a, synapsin1a and NOC2 (51, 52). Therefore, molecules targeting the above-mentioned miRNAs can be implemented in the development of a potential pharmacological agent in control of diabetes.

Esau and coworkers have used antisense oligonucleotides for 86 human miRNAs to transfect cultured human pre adipocytes and studied their ability to modulate adipocyte differentiation (53). Furthermore, they also examined expression of 254 miRNAs in differentiating adipocytes by doing miRNA based microarray analysis, as reported previously (54). Combinations of microarray data and functional assay results have identified a role for miR-143 in adipocyte differentiation. In differentiating adipocytes, increased levels of miR-143 were observed and antisense inhibition of miR-143 effectively inhibited adipocyte differentiation. In addition, protein levels of ERK5, the proposed target of miR-143 were found to be higher in antisense oligonucleotide-treated adipocytes (53). These studies indicate a role of miRNAs in adipocyte differentiation and the possibility of using them as therapeutic targets for obesity and metabolic diseases.

3.3. miRNA in neurodegenerative diseases

Neurodegeneration refers to the process of a pathological condition, affecting the neurons in a detrimental way. The clinical and pathological features of the more commonly reported neurodegenerative diseases (NDD) are all associated with progressive deterioration of the cognitive faculties of the brain. Clinical features are varied but are typical for each diagnosed disease and are

accompanied by a bleak prognosis. Pathological characteristics include atrophy, degeneration and loss of brain function, which, as the disease progresses, worsen exponentially Among many clinically identified NDD's, the majority of the attention is focused on a select few such as Alzheimer's Diseases (AD), Parkinson's Diseases (PD), Huntington's Disease (HD), and Amyotrophic Lateral Sclerosis (ALS) (55). Multiple Sclerosis (MS) also receives a lot of attention, but it is debated whether MS is truly classified as a NDD as its method of attack is directed at the myelin sheath and oligodendrocytes, rather than at the neurons themselves (55, 56). Comparatively, less work with respect to miRNA profiling in human subjects and/or cell lines has been done in this area. However, recent work on *Drosophila* and mice suggest the potential role of miRNA in neurodegenerative diseases. Bantam (ban) miRNA can play an important role in modulating the nerve cell toxicity of pathologically altered spinocerebellar ataxia (SCA3) protein, in *Drosophila* (54). This study confirms that ban miRNA helps in the prevention of neurodegeneration, caused by increased number of poly glutamate repeats in SCA3 proteins and modulates polyQ- and tau-induced neurodegeneration. In another study, by analyzing cellular purkinjee fiber specific expression of cre recombinase, Dicer gene was knocked down in cerebellar purkinjee fibers. Neuronal death was observed after 2nd week of cell specific promoter (Pcp2) activation. It was hypothesized that, neurodegeneration was caused because of Dicer knock down and down regulation of brain specific miRNA production which has potential role in neuroprotection (57). An interesting investigation on the role of miRNAs in mammalian midbrain dopaminergic neurons (DNs), reported that miR-133b, (expressed in midbrain DNs) was found to be deficient in midbrain tissues from patients with Parkinson's disease (58). This ground breaking observation specifically fires an idea about the importance of miRNAs in neuro-protection.

On the other hand, miR107 was found to be down-regulated most prominently with Alzheimer disease (AD) progression when miRNA expression profiling from the brain tissue extracted RNA samples of patients suffering from AD with varying degree of disease progression were carried out. (59). Computational analysis predicted a putative target for miR107 as beta−site amyloid precursor protein-cleaving enzyme 1 (BACE1). Further, mRNA array analysis data correlated with this, as BACE1 mRNA levels were found to be up regulated with AD progression. Taken together, the coordinated application of miRNA profiling, affymetrix microarrays, new bioinformatics predictions, *in situ* hybridization, and biochemical validation, indicated a potential role for miR-107 in neuroprotection (59). The relation between expression profiles of miR-29a, -29b-1, and -9 and BACE1 in sporadic AD patients and also in primary neuronal cultures and HeLa, SK-N-SH, HEK293, and HEK293 cell lines was reveled in an interesting work by Strooper and co investigators (60). Changes in miRNA expression profiles of sporadic AD patients revealed that the levels of several miRNAs, including miR-29a, -29b-1, and -9, potentially involved in the regulation of amyloid precursor protein (APP) and beta Secretase (BACE1) expression, were found to be decreased in diseased brain. Differential downregulation of the expression of miR-29a/b-1 cluster was observed as disease progressed (60), indicating the loss of BACE1 mRNA regulating miRNA cluster in AD development and its possible use in the development of early diagnostics. DNA arrays were analyzed to evaluate the expression of a subset of 12 miRNAs in non-demented (ND) controls and fetal brain in comparison with the AD hippocampus. miR-9 was elevated in both fetal hippocampus and AD hippocampus whereasmiR-128a found to be elevated in AD hippocampus but neither fetus nor ND controls showed increase in miR128a. miR-125b showed a trend to be increased in AD that was not statistically significant (61). In a parallel study, cultured human fetal brain-derived primary neural (HN) cells, which included both astrocytes and neurons, were treated with metal salts, such as aluminum and iron sulfates that stimulate reactive oxygen species (ROS). Remarkably, the treated HN cells with activated ROS had essentially the same changes (increased expression of miR-9, miR-128 and, to a lesser extent, miR-125b) versus controls, as were seen in the AD brain in comparison with non-demented brains (62). This datum provides evidence in support of the hypothesis of ROS influence in AD brain, through pathways specifically mediated by miRNAs. Also, miR-125b, which trends to be higher in both AD brain and in ROS-treated HN cells, is predicted to target the mRNA of synapsin I and synapsin II, and thus observed down regulation of synapsins in AD may be partially explained by miR- 125b up-regulation.

In non neuronal cells, neuron-restrictive silencer factor (NRSF)/RE-1-silencing transcription factor (REST) is found to abrogate with anomalous Huntington protein, expressed in Huntington's disease (HD), thereby silencing neuronal gene expression, after binding with RE1 repressor sequences (63). Levels of several miRNAs with upstream RE1 sites were found to be decreased in this study conducted on HD patient cortices and healthy controls, respectively. As a matter of interest, one of these bifunctional brain enriched miR-9/miR-9*, targets two components of the REST complex: miR-9 targets REST and miR-9* targets co repressor of REST (CoREST), which indicates association of miRNAs in NDDS (63). Spinocerebellar ataxia type 1 (SCA1) is caused by expansion of a translated CAG repeat in ataxin1 (ATXN1). It has been shown that inhibition of miR-19, miR-101 and miR-130, which co-regulate ataxin1 levels, enhanced the cytotoxicity of polyglutamine-expanded ATXN1 in human cerebellar purkinje cells and in other human cell lines such as HEK293T, HeLa and MCF7. (64).

In another study conducted to investigate the involvement of miRNAs in prion mediated neurodegeneration microarrays and RT-PCR were used to profile miRNA expression changes in the brains of mice infected with mouse-adapted scrapie. 15 miRNAs were found to be de-regulated during the disease processes; miR-342-3p, miR-320, let-7b, miR-328, miR-128, miR-139-5p and miR-146a were up-regulated over 2.5 fold and miR-338-3p and miR-337-3p over 2.5 fold down-regulated. Further computational analysis predicted numerous

potential gene targets of these miRNAs, including 119 genes previously determined to be also de-regulated in mouse scrapie. De-regulation of a unique subset of miRNAs suggests that a conserved, disease-specific pattern of differentially expressed miRNAs is associated with prion-induced neurodegeneration (65). All in all, above studies demonstrate that miRNAs play neuro-protective roles in neurodegenerative diseases and their expression profiling can be exploited for the development of diagnostics and/or miRNA based therapeutics. Recent advances in nanotechnology can be used to target these oligomers via the blood brain barrier (66).

3.4. miRNA in angiogenesis, chronic inflammation and vascular diseases

Angiogenesis is important in the normal development of the embryo and foetus. It also appears important to tumor formation. Angiogenesis is a normal important process in growth and development of the embryo and foetus, as well as in wound healing. However, it is also a fundamental step in the transition of tumors from a dormant state to a malignant one (67). Inflammation is a basic way in which the body reacts to an infection, irritation or other injuries, the key feature being redness, warmth, swelling and pain. Inflammation is now recognized as a type of nonspecific immune response. Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants (68, 69). It is a protective attempt by the organism to remove the injurious stimuli as well as to initiate the healing process for the tissue. Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells which are present at the site of inflammation and is characterised by simultaneous destruction and healing of the tissue from the inflammatory process. Vascular diseases are conditions that affect the blood vessels (arteries and veins) that carry blood throughout the body. Vascular disease affecting the arteries is called arterial disease e.g. atherosclerosis; those vascular conditions affecting veins are called venous diseases (56, 69). Recently, as reviewed elsewhere (69) and discussed above, miRNAs have emerged as a class of gene expression regulators that has also been linked to cancer. However, the relationship between inflammation, innate immunity, and miRNA expression is just beginning to be explored. Inflammation, a beneficial response of the host immune system is a self-limiting process under normal circumstances. In a number of conditions the state of inflammation persists for a prolonged period of time and becomes chronic ceasing to be beneficial to the host and can lead to a loss of tissue or organ function. The “chronicity” of inflammation can be understood as being the result of either the persistence of a stimulus, for example a micro-organism or allergen, or of a deregulation of the endogenous anti-inflammatory mechanisms that normally coordinate resolution (69). Endothelial cells are the specific cells present in vascular system, which forms and acts as barrier for the inward / outward flow of blood cells, biomolecules and inorganic molecules. This function is an essential attribute for the homeostasis in the vascular system. Endothelial dysfunction with up-regulated expression of stress proteins (HSPs) and cell adhesion molecules (CAMs), causes many a number of unwanted implications in various inflammatory diseases such as asthma, inflammatory bowel disease (IBD), arthritis, atherosclerosis and multiple sclerosis (MS) along sides, alterations in regular angiogenesis (70-73). Endothelial specific miRNA spectrum includes miR-let7b, miR-16, -21, -23a,-29,-100,-221,-222 and miR126, enriched in embryonic bodies derived Flk^+ cells. miR126 positively regulates many aspects of endothelial cell biology including cell migration, organization of cytoskeleton, capillary network stability and cell survival (74, 75). mir126 is found to regulate endothelial cells derived from mouse embryonic stem cells, by promoting vascular endothelial growth factor (VEGF) signaling. It has been observed that miR126 down regulates the negative regulators of the VEGF pathway, including the Sprouty-related protein (SPRED1) and phosphoinositol-3 kinase regulatory subunit 2 (PIK3R2/p85-b). Also, in this study, it was found that knockdown of miR-126 in zebrafish resulted in loss of vascular integrity and hemorrhage during embryonic development, in correlation to that of SPRED 1 up-regulation and/or inhibition of VEGF signaling (74). Targeted deletion of miR-126 resulted in leaky vessels, hemorrhaging, and partial embryonic lethality in mice. This has been attributed to a loss of vascular integrity and defects in endothelial cell proliferation, migration, and angiogenesis. The vascular abnormalities of miR-126 mutant mice resemble the consequences of diminished signaling by angiogenic growth factors, such as VEGF and FGF (75). miR-126 inhibits the expression of vascular cell adhesion molecule 1 (VCAM-1), known to mediate leukocyte adherence to endothelial cells. Thus, down regulation of miR-126 levels in endothelial cells increase TNF-α-stimulated VCAM-1 expression and thereby enhances leukocyte adherence to endothelial cells (76). These findings suggest a role of miR126 in maintaining vascular integrity, and its therapeutic implications for a variety of disorders involving abnormal angiogenesis and vascular leakage. It is interesting to see whether these miRNAs have any effect on regulating hypoxia inducing factor (HIF) dependent VEGF and/or other pro-angiogenic factor gene up regulation and further implications of them in angiogenesis.

A number of studies in relation to the role of miR155 in inflammation have been carried out. Angiotensin II type1 receptor (AT1R) is expressed in endothelial and vascular smooth muscle cells and the adverse effects of angiotensin II (Ang II) are primarily mediated through the Ang II type 1 receptor (AT1R) ; and miR155 which was found to translationally repress AT1R (77, 78). A silent mutation in locus +1166 A/C has been found to have implications in human cardiovascular disease as a result of enhanced AT (1)R activity (78). Interestingly,

this mutation found to affect the 3' untranslated region (UTR) of AT1R, thereby its interaction with miR155 cannot be possible because of interrupted base-pairing complementarity at 3' UTR as a result of the mutation. Taken together, these studies demonstrate that the AT1R and miR-155 are co-expressed and that miR-155 translationally represses the expression of AT1R *in vivo*. In another study, up-regulation of miR-155 was observed in primary murine macrophages treated with polyriboinosinic; polyribocytidylic acid (polyI:C) or the cytokine IFN-β , inhibition of JNK blocked both poly (I:C) and TNF-α_ induction of miR-155, indicating a role for MAPK signaling in the regulation of miR-155 levels (79). This observation indicates possible implications of miR-155 as a component of the inflammatory response. Similarly, LPS stimulation of mouse Raw 264.7 macrophages was found to up regulate miR155, but down regulate miR125b (80). miR-155 most probably directly targets transcript coding for several proteins involved in LPS signaling such as the Fas-associated death domain protein (FADD), IkappaB kinase epsilon (IKKepsilon), and the receptor (TNFR superfamily)-interacting serine-threonine kinase 1 (Ripk1) while enhancing TNF-α translation. On the contrary, miR-125b targets the 3'-untranslated region of TNF-α transcripts, which may be the reason for its down-regulation in response to LPS, for proper TNF-α production (80). It has been shown that miRNA 155 contributes to physiological granulocyte/monocyte (GM) expansion, in a similar manner that was observed in myeloid neoplasia (81). A possible role of miR-155 as a contributor to physiological GM expansion during inflammation and to certain pathological features associated with Acute Myeloid Leukemia (AML) has been suggested emphasizing the importance of proper miR-155 regulation in developing myeloid cells during times of inflammatory stress (81).

In addition, miR-155 is known to be required for B and T lymphocyte and dendritic cell function (82). It has also been studied that, miR155 is required for antibody production after vaccination with attenuated salmonella vaccine (83). B cells lacking miR155 were found to produce low affinity of IgG1 antibodies. Transcription factor Pu.1, was found to be over expressed in wild type B cells and has been identified as a direct target of miR-155 in B cells. Loss of Pu1 function by miR155 is the factor seemed to be responsible for low affinity IgG1 production in B cells. Thus, miR-155 is an emerging target of a broad range of inflammatory mediators and regulates lymphoid and myeloid cell functions (83). miR150 is found to be expressed in lymph node and spleen and up regulated during the development of T and B cells. miR 150 is found to play a key role, mainly in the development of B cells (84). miR424 and NFI-A are involved in Pu.1 transcription factor mediated monocyte and/or macrophage differentiation. Up regulation of miR 424 by PU.1 caused down regulation of NFI-A and further activation of differentiation specific genes such as M-CSFr, in human myeloid cell lines as well as in $CD34^+$ differentiation (85). miRNA 17-5p, 20a and 106a have been also shown to regulate monocytopoiesis (86). Another myeloid-specific miR-223 found to have implications in regulating progenitor proliferation and granulocyte differentiation and activation during inflammation (87). These reports along with increasing number of new reports indicate a role of miRNAs in mediation of chronic inflammation (63, 88-90). Overall, miR126, miR155, miR21 have a potential role in the modulation of vascular disease while miR150 and miR424 appears to play a pivotal role in B cell maturation and macrophage differentiation.

3.5. miRNA in viral infections

Although much of the work is underway, in relation to the role of miRNA in viral disease, recent reports indicate that viral miRNA can play an important role in targeting various host genes (91). Epstein Barr virus (EBV) latent membrane protein1 (LMP1) deregulates the expression of several cellular miRNAs, including miR-146a, confirmed by miRNA microarray analysis and quantitative RT PCR (92). It has been proposed that miR146a can help the virus in the induction and/or maintenance of latency by modulating innate immune responses to the virus infected host cell (93). Transactivation of miR155 in EBV transfected B cells was also observed. Here miR155, which is critical for B cell maturation and Ig production (94), was found to be activated in the presence of EBV LMP1 by NFκB, suggesting a role of miR155 in EBV-mediated transformation of B cells (94). It was found that the 3' ends of HIV-1 messenger RNAs are reportedly targeted by a cluster of cellular miRNAs including miR-28, miR-125b, miR-150, miR-223 and miR-382, which are enriched in resting CD4+ T cells, as compared to activated CD4+ T cells. This miRNA cluster has been found to have implications in maintaining the latency of HIV1 virus in resting $CD4^+$ T cells (95). This finding can help in overcoming major barrier against highly active antiretroviral therapy (HAART) by manipulating cellular miRNAs. HIV-1 Tar miRNA's effect on cellular gene expression was found by cloning and sequencing 5' and 3' ends of TAR miRNA and computational study for complementary genes. The expression of TAR microRNA protects infected cells from apoptosis and acts by down-regulating cellular genes involved in apoptosis. Specifically, the miRNA down-regulates Excision Repair Cross Complementing-group 1 (ERCC1) and Intermediate Early Response3 (IER3), protecting the cell from apoptosis, thereby helping in maintaining latency of the virus (96). Hepatitis B viral genome is also found to encode one miRNA for the regulation of its own genome. Presence of no putative sequence in human genome, however gives an idea that it cannot help the virus in interacting with the host genome (97, 98).

A large spectrum of 12 miRNAs was identified in Kaposi's sarcoma associated herpes virus genome. By doing gene expression profiling in cells stably expressing KSHV-encoded miRNAs, it was found that, expression profiles of nearly 81 genes g*et al*tered (99) . Out of all these genes, 3 genes were found to consistently decrease protein levels of thrombospondin 1 (THBS1), a major regulator of cell adhesion, migration, and angiogenesis by a factor greater than10-fold, suggesting that KSHV-encoded miRNAs may contribute directly to pathogenesis by down-

regulation of THBS1 (99). A recent study on cervical cancer tissues and cervical cancer-derived cell lines containing oncogenic human papilloma virus (HPVs), displayed reduced expression of tumor-suppressive miR-34a. The reduction of miR-34a expression in organotypic tissue correlates with the early productive phase and is attributed to the expression of viral E6, which destabilizes a known miR-34a transactivator, P53 (100). Liver specific miR-122, has been implicated in the control of hepatitis C virus (HCV) RNA replication and its response to interferon (IFN) in human hepatoma cells (101, 102). In summary, miRNAs, including miR146a,-155, -28, -125b, -150, -223, -122 and -382 and several others may have critical roles during the propagation and/or inhibition of viral replication in important viral diseases such as AIDS and hepatitis. On the other hand, some viruses like HIV and KSHV are capable of encoding miRNA that helps in their propagation, giving inspiration for designing new antagomir based therapeutics. Further work in this area could open the doors for miRNA based drugs.

4. ROLE OF MIRNAS IN ANTICANCER DRUG RESISTANCE

Although significant advances have been made in the treatment of various types of cancer; drug resistance remains a major clinical obstacle to successful treatment and leads to poor prognosis for the patients. One of the major cancer treatment methods is chemotherapy which often fails because of multidrug resistance (MDR) of cancer cells either intrinsic or acquired after initial therapeutic round (103). The anticancer drug resistance mechanisms have been broadly explored, yet more studies need to be done. MDR was initially thought to arise from molecular changes inhibiting the drug-target interaction, represented by over expression of drug efflux pumps such as P-glycoprotein (P-gp, a product of *MDR-1* gene) or intracellular detoxifiers such as antioxidants (*e.g.*, glutathione) in drug-resistant tumor cells (103-105) Other factors acting downstream of the initial drug-induced insult have been proposed to play an important role in the development of MDR such as enhanced DNA repair activity, defective apoptosis pathway, etc (106). Anti-apoptotic proteins such as BCL2 and survivin have also been found to be responsible for drug resistance (23, 107-109). As reviewed elsewhere, (110) the molecular genetic basis of sensitivity and resistance to cancer therapeutics is complex, involving multiple processes such as drug transport, drug metabolism, DNA repair, and apoptosis. Since DNA, mRNA, and proteins remained the traditional focus as targets and modulators chemotherapy, therefore, mutations, copy number changes, and epigenetic variables at the DNA level and expression changes at the mRNA and protein levels have been widely studied to probe mechanisms that determine the pharmacologic response. miRNAs are known to play important roles in the regulation of normal gene expression for developmental timing, cell proliferation, and apoptosis. In addition, aberrant miRNA expression is strongly implicated in cancer genesis and progression (110-112). It has been indicated that altered miRNA level resulted from mutation or aberrant expression is correlated with various human cancers. It was observed that the abnormally expressed miRNAs in human cancers, target transcripts of essential protein-coding genes involved in tumorigenesis, including oncogenes and tumor-suppressor genes (113). Recently, as a part of the Molecular Targets Program aimed at elucidating molecular targets and understanding mechanisms of chemo sensitivity and chemo resistance, studies were carried out systematically. The expression levels of miRNAs in the NCI- 60 (a panel of 60 diverse human cancer cell lines) were measured and analyzed in combination with other molecular profiling data sets in order to explore miRNAs as targets and modulators of the drug resistance mechanisms in cancer (110, 114). Accumulating evidence (reviewed in 110,115) reveals an important role of miRNAs in anticancer drug resistance and miRNA expression profiling can be correlated with the development of anticancer drug resistance.

Breast cancer is the most common cancer in women. Tamoxifen blocks the effects of estrogen on breast cancer cells, and the current standard adjuvant therapy in women with estrogen receptor positive breast cancer. Considering that about 30% of these tumors are resistant to tamoxifen, importantly a recent study (116) showed significantly increased expression of 8 microRNAs and down regulation of 7 microRNAs in a tamoxifen-resistant breast cancer cell line compared to the tamoxifen-sensitive cell line. It also revealed a relationship between increased tamoxifen resistance and reduced level of p27 (Kip1) by augmenting miR-221/222 expression. Another study suggested that suppression of mir-21 using antisense oligonucleotides sensitized MCF7 cells to anticancer drug topotecan (117).

Gastric cancer is projected as a second major cancer (118) and chemotherapy remains the primary treatment for both resectable and advanced gastric cancer as to improving overall survival and quality of life for patients. In SGC7901/VCR cells there is down-regulation of miR-16 as well as miR-15b, a homologue of miR-15a (103). Furthermore, the study suggests that miR-15b and miR-16 directly regulate BCL2 expression, thereby modulating the MDR in human gastric cancer cells. A surprising number of diverse miRNAs' expression levels were found to be altered in cholangiocarcinoma and colon cancer cells, treated with gemcitabine and 5-FU respectively (119,120). Moreover, modulation of some miRNAs resulted in an increase in the sensitivity of cholangiocarcinoma cells to gemcitabine (119).

In advanced ovarian cancer patients chemotherapy is again a preferred approach but the development of drug resistance prevents the successful long-term treatment. Sorrentino *et al* have shown (121) that ovarian cancer drug resistance is associated with a distinct miRNA fingerprint. Six miRNAs (let-7e, miR-30c, miR-125b, miR-130a and miR-335) were always diversely expressed in a panel of paclitaxel- (A2780TAX, A2780TC1 and A2780TC3) and cisplatin resistant (A2780CIS) cells. miR-125b, was found to be down-regulated only in A2780TAX and up-regulated in the other cell lines whereas miR-30c, miR-130a and miR-335 were down-regulated in

all the resistant cell lines and thereby suggesting a direct involvement in the development of chemo resistance. The study further revealed that miR-130a, targets the expression of the resistant factor M-CSF. From the study, miRNA microarrays could represent a promising prognostic tool to monitor the chemotherapy outcome. As with other findings further clinical studies are now needed to test if these findings will be confirmed in translational studies in ovarian cancer patients.

5. SUMMARY AND PERSPECTIVE

More than a decade after its discovery, miRNA has become a crucial aspect in gene regulation. Many breakthroughs have related the involvement of miRNA in prevention and progression of a number of human diseases including cancer, neurodegenerative diseases, diabetes and in chronic inflammatory diseases. Differential expression profiling studies, focused on the expression of miRNAs in effected tissues in relation to normal tissues indicate the power of miRNA in gene regulation in cell growth and apoptosis. *In vitro* and/or *in vivo* stability and total average half life of miRNA over mRNA give an advantage to use them as potential diagnostic markers and therapeutic agents. However, therapeutic delivery of these oligomers to the specified malignant and/or diseased site poses problems. Moreover, M Kozac in a recent review (122) raised the concerns regarding the proposed hypothesis and/or experimental design related to some of the recent findings on methods of action of miRNAs. The scientific ideas ('faulty old ideas") behind the discoveries related to mechanisms that regulate miRNA's effect on mRNA translation have been questioned along with the use of old faulty tools. In agreement to this, there are some questions need to be addressed and better experimental set ups are urgently needed. Nevertheless, taken in a positive prospective, majority of the methods and findings some or the other way pacts miRNA regulation control in the generation of a gene product. These can be overcome by using suitable drug carriers. Recent advancement in nanotechnology field can be a better choice for the delivery of these oligomers. In the future, detailed work in the field of miRNA biomarkers and in drug delivery can open a vast opportunities for Biomedical research and Biopharma industry.

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