Cancer and neurodegenerative disorders: pathogenic convergence through microRNA regulation

Ujwal Kumar* and M K Aneebuddin

1Global College of Pharmacy, Moinabad, Hyderabad, Telangana State, India
2Department of Pharmaceutics, Shadan College of Pharmacy, Telangana State, India

ABSTRACT

Despite the fact that cancer and neurodegenerative disorders are two separate diseases with unique pathology, it can be construed from emerging pieces of evidence that these two types of diseases share common mechanisms of genetic and molecular abnormalities. Recent studies and current understanding show that individual microRNAs (miRNAs) may be involved in the pathology of these two apparently diverse diseases, indicating that there is a common mechanism that leads to the theory of dysregulation in gene expression at the post-transcriptional level. Several miRNA-based therapeutic approaches have shown efficacy in the modulation of activities of miRNAs, indicating their potential to treat a number of pathological conditions. On the same lines, the role of miRNAs in the converging pathways of leading both diseases suggests good prospects for developing common therapeutic strategies for both diseases. Not only for therapeutic approaches, but the miRNAs also dysregulated in both diseases might be promingly viewed as uniquely informative diagnostic markers. In this paper, we review recent studies on the miRNAs involved in both cancer and neurodegenerative diseases.

Keywords: microRNA; miRNA-driven theranostic strategies; neurodegenerative disorders; Neurotransmission.

INTRODUCTION

Cancer and neurodegenerative disorders are viewed as a broad class of diseases that are difficult to manage in the aging population of the world. Although cancer cells and neurons are entirely different, with cancer cells dividing rapidly and the neurons relatively non-replicating and quiescent, recent studies and evidence support common genetic mechanisms leading to dysregulated growth of cancer cells and the neurodegenerative disease progression. Several types of genes and their mutations in biological processes such as DNA repair pathways, regulation of the cell cycle, protein turnover, autophagy, and oxidative stress have been involved in each of these seemingly disparate disorders (1-5). Recent studies have shown that changes in microRNA (miRNA)-based regulation in biological systems have emerged as potential regulators of both neurodegenerative and cancer pathologies. Individual miRNAs are of particular interest because they play a critical role in the instigation and progression of both malignant neoplasias and neurodegenerative diseases. The implication of miRNAs in these two conditions is attributed to either regulating common pathways linked with both diseases or targeting specific genes unique to each disease. The miRNAs are non-coding, short RNAs that are formed endogenously to regulate the expression of various genes involved in diverse biological functions. These miRNAs bind to sequences in the 3′ non-translated regions of expressed mRNAs, which primarily result in repression of protein translation or degradation of the mRNA transcript. Short, 7-nucleotide 'seed sequence' determines the specificity of miRNA targets by allowing for both approaches. Multiple miRNAs targeting a single mRNA transcript, as well as a broad spectrum of targets for specific miRNAs. Over a period of decades, studies demonstrate that the pathogenesis of various diseases is associated with dysregulation of microRNA expression (5-8). The miRNAs have been thoroughly explored as potential diagnostic markers as well as therapeutic targets and promising theranostic agents in near future. Since miRNA regulation in the pathogenesis of cancer and
neurodegenerative diseases meets a common pathway, targeting this miRNA regulation paves avenues for the common therapeutic and diagnostic strategy for the two diseases. In this review, we present an overview of the most recent studies on miRNAs associated with neurodegenerative and cancer diseases.

miRNAs and common pathways in cancer and neurodegenerative disease

miRNAs have been implicated as potential regulators of APP, which is an integral membrane protein and related to both Alzheimer’s disease and cancer growth. Several studies show that increased expression of APP is associated with AD, with evidence of APP concentration at neuronal synapses, and is the key component of AD-associated amyloid plaques that are formed after proteolysis. In the case of somatic cells, it was observed that APP increases epithelial cell proliferation and migration, however, the mechanism is yet to be fully elucidated. In addition, several reports have data indicating overexpression of APP in various cancers, including pancreatic, esophageal, oral cavity, thyroid, neuroendocrine, and colorectal cancers. These results highlight the important function that APP may play in cancer pathogenesis. Numerous miRNAs, including miR-20a miR-17-5p, and miR-106b, were reported that regulate APP in vitro by reducing the expression of endogenous APP through transient transfection in HeLa cells (9-10). In the same study, researchers discovered a decrease in miR-106b expression in the brain tissue of Alzheimer’s disease patients when compared to controls. In yet another study that involved Caenorhabditis elegans, a decrease in expression of APP ortholog, APL-1 by let-7 family miRNAs was reported, thus providing clear in-vivo proof of APP regulation by the let-7 family of miRNAs. Besides the aforementioned examples, it is believed that miR-29a/b-1 indirectly regulates APP function by direct targeting BACE1/b-secretase. BACE1, an aspartic acid protease, is involved in a crucial role in the pathophysiology of AD, and indication shows enhanced BACE1 expression, may result in improper cleavage of APP and higher accumulation of amyloid b-peptides in patients having sporadic AD (11-13). In one in-vitro study, downregulation of BACE1 expression by miR-29a/b-1 cluster was reported confirming the reduction information amyloid b-peptides in a reversible manner. The same study further concluded that these miRNAs levels are significantly decreased in AD patients with dementia components who express unusually high levels of BACE1. As a result of the evidence presented above, it appears that altering the expression of APP, as well as the abnormal expression of miRNAs, can play a significant role in the growth of AD and cancer. Ataxia-telangiectasia (AT) is a neurodegenerative disorder occurring due to mutations of either ATM or ataxia-telangiectasia and Rad3 related (ATR) protein kinases. ATM and ATR collectively act as important regulators of double-strand break DNA repair by phosphorylation of crucial protein substrates participating in downstream signals to massive networks of DNA repair. ATM and ATR act as tumor suppressor genes in somatic cells when they are activated, mainly through apoptosis and cell cycle arrest (14-16). Several types of tumors show Mutations in ATM and ATR, with approximately 40% of patients homozygous for ATM mutations that develop into cancer (17). These findings imply that ATM and ATR have a crucial role in carcinogenesis as well. In recent studies, it was found that the miR-421 targets ATM protein as a regulatory target (18), and miR-421 was shown to be highly expressed in both gastrointestinal cancer tissues as well as a cell line from diffuse large B-cell lymphoma. Indeed the miR-421 objectives ATM protein expression suggests that this miRNA may have a critical role in the pathogenesis of AT as well as cancer. PTEN is a tumor suppressor that inhibits activation of the PI3K/Akt/ mTOR signaling pathway which is associated with enhanced cell growth and survival in a score of human cancers. PTEN signaling is indeed linked to Parkinson’s disease (PD) development via the regulation of two genes that give neuronal protection from oxidative stress, Parkinson’s disease 7 (PARK7, otherwise referred to as DJ-1) as well as PTEN-persuade putative kinase (PINK1) (19). Established evidence from the literature suggests that PTEN is a regulatory target for the number of miRNAs-particularly, PTEN down-regulation by miRNA mediation through miR-21 activity and a significant rise in miR-21 levels evident in a number of human tumors (20-22). Another study reported a causal link between miR-106b and PTEN downregulation. These illustrations suggest that aberrant miRNAs expression can be associated with both neurodegenerative disease and cancer pathologies by down-regulation of PTEN expression.

miRNA regulation of pathways unique to cancer or neurodegenerative disease

Examples up till now have shown that an individual miRNA can target genes representing common pathways of both neurodegenerative diseases and cancer. Several other studies have reported that a single miRNA can also be associated with both cancer and neurodegenerative disorders by targeting different pathways, one being cancer pathology and the other for neurodegenerative diseases. For instance, another study proposes that miR-133b may play a vital role in PD by suppressing the PITX3 transcription factor expression. They reported that miR-133b acts by a negative feedback loop and suppresses the expression of PITX3, which in turn up-regulates the expression of miR-133b to modulate the PITX3 expression in dopaminergic neurons (DNS) in the midbrain. Additional supporting evidence demonstrates that miR-133b expression is severely reduced in PD patients’ midbrain tissue, implying that miR-133b is important in PD. MiR-133b has been found to be down-regulated in a variety of malignancies, including colon, lung, and esophageal cancers, which have implications for carcinogenesis (23-20). Among the miR-133b
targets reported in cancer are genes associated with pro-survival signals such as BCL2-like 2 (BCL2L2), oncogenic actin-binding factors such as fascin homolog 1 (FSCN1), myeloid cell leukemia sequence 1 (MCL1, also known as BCL2L3), and the met proto-oncogene receptor tyrosine kinase (MET). These instances show that implication of miR-133b has a role in the pathogenesis of both neurodegeneration and cancer by targeting different disease-specific pathways. One more miRNA, miR-124a is reportedly involved in tumorogenesis through the regulation of the expression of the retinoblastoma (RB) tumor suppressor gene and cyclin-dependent kinase 6 (CDK6) oncogene. According to one study, overexpression of miR-124a resulted in a neuron-specific expression profile in HeLa cells. From the affected areas of the brains of patients with idiopathic PD, isolated DNS showed deregulated genes which were also found in about one-fifth of down-regulated genes. In another study, 27 validated targets of miR-124a were identified, out of which eight were deregulated in PD neurons. Results of these studies correlated well with results from the MIRECORDS database, which demonstrate that validated miR-124 targets to the tune of 24% are alternatively regulated in PD. While further investigation is needed to establish the role of each of miR-124a in the pathologies of both neurodegenerative disorders and cancer.

CONCLUSION

The above-cited examples draw attention to the multiple roles that individual miRNAs can play in the regulation of both distinct and common pathways associated with the pathogenesis of neurodegenerative and cancer diseases. In order to fully understand the after-effects of aberrant miRNA expression, further thorough research is needed. This will help in subsequent research on the roles of miRNA in the development and initiation of both diseases. The common pathway of regulatory mechanisms of both cancer and neurodegenerative diseases undoubtedly suggests that such research endeavors will not only shed light on the association between the initiation and progression of two diseases but will also establish an experimental basis for common miRNA-driven theranostic strategies.

REFERENCES


