Abstract

MicroRNAs (miRNAs) are a class of small RNA molecules that interfere in gene expression regulation. These molecules repress their targets post-transcriptionally through their seed sequence, resulting in mRNA degradation. The outcome of miRNA-mediated changes depends on different parameters such as cell type and tissue context as well as pathophysiological status in the interaction area, hence a vast spectrum of usefulness as a therapeutic agent is considered. In silico studies, besides experimental approaches, reveal further possible applications for miRNAs as a part of a more complex entity in cellular pathways through the following roles:

- As a part of a more sophisticated competitive regulatory system in promoting a regulon-like network involving in disease pathogenesis and clinical outcomes.
- As a part of a chemo-attractant immunogenic element to non-self-cells by pushing the gene expression machinery to present surface markers of these cells to the immune system.
- As a part of a signaling pathway which facilitates apoptosis through binding to the most vulnerable and highly active genomics, transcriptomics and proteomics regions in abnormal cells.

In this review, we discuss these less-noticed therapeutic potentials of miRNAs which may result in novel treatment options in different diseases.

Keywords: microRNA; Pharmacogenomics; Epigenetics; Disease therapy

Introduction

Background

MicroRNAs (miRNAs) are a class of small RNA molecules (about 22 bp) which can regulate gene expression [1–3]. miRNAs repress their targets post-transcriptionally through their seed sequence, nucleotides 2-8 at 5’-end, resulting in mRNA degradation [4,5]. These molecules are considered as one of the most abundant regulatory gene groups in multicellular organisms, playing important roles in many fundamental cellular processes. Hundreds of miRNAs have been identified recently and the deregulation of miRNA expression has been shown in many cancers [6,7].

MicroRNAs regulate gene expression at post-transcriptional stage through duplex formation between relevant sequences within the miRNA and target messenger RNA, yet the complementarity as the main determinant in type and process of regulation. [7, 8] The end result of the miRNA-mediated modifications depends on different parameters such as cell type and tissue context as well as pathophysiological status in the interaction area [6-8]. They show a vast spectrum of usefulness in the treatment of disorders as therapeutic or alleviating agent. When the binding is associated with major or most complementarily degree to target region of the mRNA, cleavage and degradation of the target transcript occurred at its most desired level [9-11]. This type of regulation mechanism shows irreversible outcomes, with predictable definite end results through crucial pairing of the 5’end nucleotides, considering as an important element of the miRNA-regulatory network [12]. Increasing evidences suggest miRNAs as major influencing element in gene expressions yet conferring robustness to biological processes which regulates ballottement in transcript copy number [13-14].

These activities are associated with critical consequences in all molecular and cellular streams throughout the normal development and physiology, disease susceptibility and involvement, and even evolutionary happenings. In fact, these elements would consider as prognostic and diagnostic biomarkers and even treatment tools in vital cellular and tissue specific processes both in disease and health state. In this brief, we take a look at all these functions besides defining some new potential functions to miRNAs.
MicroRNAs as biomarkers

The successful diagnosis and effective management of diseases highly depends on the early finding of reliable clues including biomarkers before the clinical stage, during the disease progress and after diagnosis establishment.

On the other hand, the simple straight sequence events, may not explain all cellular and molecular vital mechanisms of the organism and now we know a set of epigenetic processes and findings with serious cell fate interference through elements like miRNAs and so on [15]. In fact, epigenetic variations play major roles in switching between human body susceptibility to homeostasis or illnesses. Some variations show etiologic effects through direct or indirect interventions like gene expression modifications. Aberrant gene expression networks may lead to malignancy initiation, promotion and progression and biomarkers like miRNAs may be a help in patients’ monitoring in these situations [16].

To find the early signs of chaos in cell regulatory system, some elements as prognostic biomarkers should be monitored in vulnerable individuals. Early screening of colon cancer for example allows effective management in initiative stages diminishing the mortality and morbidity. On the other hand, previous studies indicate that miRNAs may be the potential diagnostic biomarkers of lung cancer and have relatively high diagnostic value to discriminate the nature of pulmonary nodules. Recent studies showed miRNAs may play a role as distinctive tool between two groups of malignant and benign disorders in these malignancies yet conventional screening work up of the disease either lack sensitivity or require some invasive procedures to patients respectively, hence we need much sensitive, least invasive tools like epigenetic biomarkers [17,18]. A similar situation may found in pancreatic cancer with most asymptomatic early courses and undetectable underlying process which need sensitive and specific biomarker of epigenetic sort [19]. Importance and application of epigenetic tools like miRNAs in this area is not limited to malignancies but in other disorders like Osteoporosis and infections such as sepsis they work as severity index [20,21]. It should be noted that prognostic and diagnostic applications of miRNAs are not limited to somatic disorders, but also, they have been used as biomarkers in psychological conditions like depression [22].

Generally, the importance of reliable and powerful epigenetic tool in accurate and early diagnosis is obvious through all aforementioned situations, conclusively different groups of miRNAs may be candidate with their potentials as novel class of non-invasive biomarker set.

MicroRNAs as treatment tools

In new era, new landscapes on disease treatments appeared focusing on less invasive and more effective mechanisms through highly specialized targets. These modern approaches have considered for severe diseases such as malignancies, cardiovascular and auto-immune or infective disorders. Recent drug developments present a new class of nucleic-acid-based molecules, such as antisense oligonucleotides, ribozymes, short interfering RNA (siRNA), and microRNA (miRNA) [23] through molecular activity modification [antimiRs, blockmiRs] [5] or cell microsecretome [24].

There are also powerful potentials for miRNA therapy in embryonic stage of development through mRNA translation regulation and miRNA maturation in embryonic stem cells. One may consider such a potential opportunity as effective mechanism in prenatal interventional therapy at molecular level to prevent cancerous transformations in next life stages [25].

MicroRNAs as regulatory tools

Specific binding of miRNAs through complementary sequences to various mRNAs, results in mRNA degradation or translational modifications and gene expression regulation which may show a vast spectrum of contribution to cell development, differentiation, and some ominous events like carcinogenesis. Thousands of recorded entries in the miR Registry Database with control potential over 30% of human genes revealed the hidden but strong ability of these elements in cellular interactions network.

MicroRNAs are highly specific to different tissue types and even for single cell type within the same tissue; hence one may see unique intervention pattern with valuable function in clinical applications as a strong switch between health and illness. Some studies showed that impaired miRNA-biogenesis and its sequential genomic or epigenetic alterations may result in an imbalance in the proto-oncogenic or tumor suppressive role of miRNAs with a predilection to tumorigenesis. Authors showed an association between miR-21 up-regulation with over 92% of the gastric cancer cases. In contrast to miR-21, expressions of other microRNAs have been reported to down-regulate in gastric cancer [22]. On the other hand microRNAs are highly expressed in central nervous system and may consider as extremely potent and dynamic regulatory mechanism to brain proteins which demonstrate critical role in basic neuronal events like metabolism, proliferation, and apoptosis [26].

All abovementioned findings suggest that miRNAs network acts as highly dynamic complex system of specific and sensitive molecules with the ability of direct and indirect wide spectrum interactions with many important events within a cell all over its life span; hence a suitable candidate for cell fate and function.

New Insights

In addition to all aforementioned viewpoints for miRNAs functions in the body, in silico studies, in association with in vitro and in vivo approaches, can reveal possible further applications for them as a part of more complex entity in cellular pathways.

miRNAs may work as a part of a highly sophisticated and interactive regulatory molecular network in the form of an integrated framework and regulon-like system which involves in disease pathogenesis or susceptibility and clinical consequences [27,28].

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It has been shown that seed length is not simply linked to miRNA differential expression level between carcinomatous and normal tissues. There is a delicate linear association between miRNA expression and folding modifications through changes in seed region length. Some studies showed more miRNAs being differentially expressed as seed region length increased [29]. These findings showed that analyzed seed sequences may show different active sites through unique long enough seed sequences and there may be many chimeric and spatial variants within a single seed sequence which shows relevancy to different regions in different target sites.

Through analyzing of thousands of reproducible chimeras, pairing to the miRNA seed predominant motif, unexpectedly, additional pairing possibilities have been found to more potential targets, dispersed throughout the genome which leads to a complicated puzzle of targets by members of miRNA families [29].

Some other investigators showed that Canonical 6-nt sites in miRNAs, interfere with the affinity of the molecule to targets and represent a competitive pattern of interaction with variant potency of epigenetics phenomena [31] and make a strong potential for wide spectrum of outputs in the form of preliminary new visions into the stoichiometric relationship between miRNAs and target interaction frequencies, target-site spatial conformation, and strength of their affinities. On the other hand, like other nuclear elements, A-to-I editing process in miRNAs may modify its cleavage specifications result in altered target sites [32] and even directly changes the specificity and sensitivity of the molecule which provides a different pattern of affinity and ever-known functions.

Someone could imagine that the modified or non-modified miRNAs have the potential to be fused temporarily or permanently with other small secretome elements, together with specific double- or multiple stranded binding partner proteins, produce miRNAs high plasticity through different reactions and functions.

The variations in miRNA-mRNA binding states, ends in variation in intensity and selection of binding not only in single target but also in multiple locations throughout the entire genome, hence multiplex effects in different capacities for mRNA repression expected via elective re-arrangement of seed sequences. This multiplicity may happen both through linear sequence and also folding angles and topology within the critical region of the molecule.

miRNAs may show themselves as a part of chemo-attractant immune-genic or immune-lytic system which reacts to non-self-cells through nuclear mechanisms. These mechanisms may involve promoting the gene expression machinery to present identifiable and distinguishing cell surface markers to recognize by defense system. This event may facilitate cytotoxic processes and immune surveillance effector mechanisms within the tumor generated microenvironment around cells and tissues.

During the times many different mechanisms have been described to control gene expression especially those involved in the immune system reactions and interference by the epigenetic elements like miRNAs as a part of a signaling pathway which facilitate apoptosis through binding to the most vulnerable and highly active genomics, transcriptomics and proteomics regions in abnormal cells [30,31].

The above-mentioned facts and findings, may considered as a commence state to impose a kind of therapeutic force on native immune system in recognition and destruction of invaders, by inducing the target cells to show their hidden identity through cell surface markers in post-transcriptional regulatory events [32,33].

These findings may notify the potential of interfering with tumor cells behavior through manipulating the miRNAs secretory profile throughout the life of invader malignant cells.

Finally one may conclude the miRNAs diverse profile through all cells and tissues in health and disease state, as an excellent opportunity to discover new frontiers not only in disorders prognosis, diagnosis and treatment options, but also in more deep modern sights in extra roles as a sophisticated competitive regulatory system, chemo-attractant immunogenic system in reaction to invaders, and also the leader of signaling pathway promotion or inhibition in different states.

References

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