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Review Article

MicroRNAs in Multiple Myeloma: A Glance into their Potential as an Anticancer Treatment Option

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Abstract

Multiple Myeloma (MM) is a malignant B neoplasm that can be characterized as a plasma cell dyscrasia in the bone marrow. Though there has been a significant improvement in the prognosis of the disease in the past decade, it is still incurable, as most patients relapse or become refractory to standard treatment. MicroRNAs (miRNAs) are short, single-stranded, highly conserved, non-coding RNAs that play a vital role in the post-transcriptional regulation of gene expression. Over the past decade, miRNAs have been investigated to see the potential impacts on hematological malignancies such as MM. Since their discovery in 1993, a significant volume of work has been done to figure out the Role of miRNAs in controlling MM. MicroRNAs can upregulate or downregulate the expression of a gene, and their Dysregulation is associated with clinical disease. They play a significant role in cellular signaling and various biological processes like cellular proliferation, aging, maturation, and apoptosis. They are critical to the normal functioning and development of the human body. This review will provide insight into the roles that miRNAs play in general cancer cell biology with a particular focus on MM, its clinical course, and management and highlight potential treatment options for using miRNA for the treatment of MM. Tumor suppressor microRNAs (TS miRNAs) and oncogenic microRNAs (Onco miRNAs) and their significance in the development and treatment of MM are also discussed. The use of miRNA in distinguishing MGUS (monoclonal gammopathy of undetermined significance) from MM is also discussed, and a possibility to prevent the progression of MGUS to MM is highlighted in this review.

ABBREVIATIONS

MM: Multiple Myeloma; miRNA: MicroRNA; TS-miRNA: Tumor Suppressor MicroRNA; OncomiR: Oncogenic MicroRNA; MGUS: Monoclonal gammopathy of undetermined significance; SMM: Smoldering Multiple Myeloma; DOX: Doxorubicin; Dex: Dexamethasone

INTRODUCTION

Multiple Myeloma (MM) is a hematological malignancy, categorized by the World Health Organization (WHO) as a plasma cell (P.C.) neoplasm. Normal plasma cells in the bone marrow transform into malignant myeloma cells in this malignancy, producing abundant immunoglobulin referred to as M-protein or monoclonal protein. The annual incidence of MM is 6-7/100,000 worldwide and accounts for 1% of all cancers [1]. In the past decade, there has been tremendous improvement in the treatment outcomes and overall survival rate using immunomodulatory drugs and proteasome inhibitors. However, MM remains a significant cause of mortality, morbidity, and incurable disease with unpredictable refractory mechanisms, partly due to chemoresistance [2].

Further studies in MM and corresponding new therapeutic strategies are urgently required. Since discovering miRNAs, their use in cancer treatment has been an area of particular interest. In this review, we study the microRNAs, particularly their role in cancer biology and the treatment of MM.

MicroRNAs (miRNAs) play a vital role in the post-transcriptional regulation and expression of genes and silence mature messenger RNA (mRNA) transcripts within the human body. MicroRNAs bind to the mRNA of interest and have a silencing effect, which leads to the suppression of target genes. Their perturbations are implicated in the pathogenesis of the human disease [3]. MicroRNA molecules are sequences of about

21-24 nucleotides in length that downregulate the expression of genes by binding in a complementary fashion to mature mRNA transcripts (Figure1). miRNAs are transcribed by RNA polymerase II and III and are vital in cellular communication. Binding can be perfect or imperfect, but binding is often imperfect in humans, which regulates gene expression by blocking the translation of the respective mRNA transcript into a functional protein [4].

In this regulatory pathway, binding of the miRNA molecule to the mRNA transcript typically occurs in the 3' untranslated region (3' UTR), an exonic region of the gene that does not code for protein, and due to the nature of the binding, the transcript is physically obstructed from being translated into a polypeptide. Perfect binding is less common but will typically result in the miRNA binding in the center of the mRNA transcript, triggering endonucleolytic cleavage of the mRNA transcript [3,5], which is typically carried out by the 3'-5' nuclear exosome or endonucleases. These inherent biological properties of miRNAs are essential to understand, as they have been proven to be of clinical importance for the treatment of various types of cancer and for developing more effective live attenuated vaccines in the field of immunology as well [6].

As miRNAs are typically highly conserved across a wide variety of vertebrates, this is represented by the fact that humans and other organisms, such as *Caenorhabditis elegans,* have miRNAs that provide similar functions [7]. For example, *Lin-4* and *Let-7* were the first miRNAs discovered in *C. elegans* in 1993. A common group of functional miRNAs in humans and lower order vertebrates alike will likely increase the flexibility of research and cut down on the number of miRNAs from which to test, opening new avenues in oncological research. The downregulate gene expression is also essential, especially when designing synthetic miRNAs to target an mRNA transcript of a known sequence.

While most miRNA silencing has been shown to occur in the cell's cytoplasm, evidence supports nuclear silencing [8], indicating that one type of treatment will likely not be sufficient for all types of miRNA. Determining this information is essential when designing miRNAs that can silence gene expression.

More recently, the Role of miRNAs has been at the forefront of scientific discussions in several cancers, including MM. Although the disease typically targets the elderly and shows twice the preference for African American descent, MM can be acquired at virtually any age [7]. Myeloma cells are post-germinal B-lineage lymphocytes that become monoclonal plasma cells and are often identified by the expression of CD38 and CD138 antigens. This cancer leads to a weak immune system; the compromised plasma cells often lead to stimulation of osteoclasts, and this leads to osteolytic lesions of bones that lack the structural integrity present in healthy individuals; and a decrease in the number of normal cells in bone marrow results in immunocompromise, low blood counts, anemia, and thrombocytopenia [9]. While normally dealt with using novel chemotherapy drugs [10], miRNAs to combat this type of cancer have been proven to be significant innovation at the research level [7].

Mutations in healthy cells, mainly afflicting either the tumor suppressor genes or protooncogenes, lead to a series of events in the process of oncogenesis and are responsible for the cells that are discohesive and responsible for invasion [7]. Specifically, mutations in KRAS, NRAS, BRAF, FAM46C, TP53, and DIS3 were observed in subclonal populations of MM, and some of these multiple mutations were observed within the same pathway

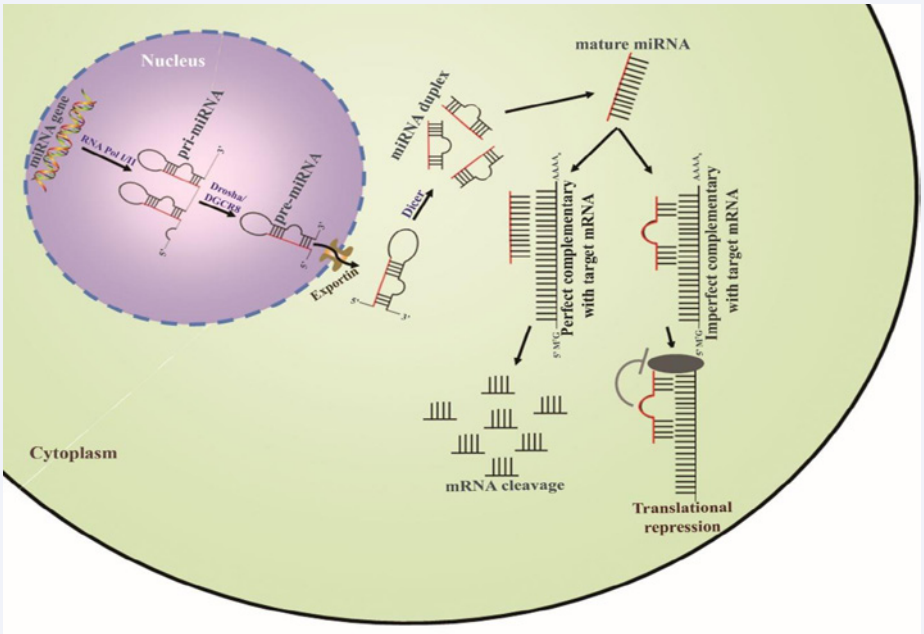

Figure 1 miRNAs can bind to target mRNA transcripts in an entirely complimentary (perfect) or partially complementary (imperfect) nature, and while binding takes place predominantly in the 3' UTR in humans and animals, the type of binding will determine the mode of silencing. Perfect binding will lead to mRNA degradation by the 3'-5' nuclear exosome complex or 5'-3' endonucleases, and imperfect binding will block translation, resulting in no expressed final protein product.

in one patient, contributing to the limited response to targeted chemotherapy [11].

Malignant tumor cells utilize miRNAs that play an oncogenic role, whereas regulatory miRNAs in the human body that defend against cancer cells act as tumor suppressors. Most organisms have been shown to use miRNAs to regulate gene expression within the genome. Still, more research has uncovered that tumor cells have their supply of miRNAs that contribute to cancer's ability to proliferate and metastasize [8]. Specifically, for MM, the use of miRNAs is paramount for properties such as angiogenesis, which contributes to the versatility and danger of the disease. Let-7 miRNAs, initially discovered in *C. elegans*, are also contained within the human genome and be at altered levels in cancer patients, including MM [7]. Targeting these miRNAs and removing the tumor cells' self-independence will likely become a clinical treatment option as more information is uncovered about how miRNAs are utilized.

RNA interference (RNA*i*) is the general term for the downregulation of gene expression using targeted mature mRNA transcripts, and miRNAs are responsible for a large portion of this process in higher-order multicellular organisms such as humans. Fire et al., in their experiment on RNA interference, found that small fragments of double-stranded RNA (dsRNA) effectively shut down the expression of a gene by the destruction of mRNA [12]. The double-stranded short fragments were found to be more effective in silencing the genes when compared to the single-stranded RNA (ssRNA) fragments described earlier and fewer fragments were needed. This groundbreaking discovery has opened up new avenues in cancer biology and treatment [12]. RNA interference can be used to treat cancer by identifying dominant signaling pathways and involved genes and targeting therapy against them. The treatment will be individualized and targeted to disrupt cancer signaling pathways [13].

Role of MicroRNA in Cancer Biology

In the past decade, miRNAs have emerged in cell biology as an essential component for facilitating tumor growth, invasion, angiogenesis, and immune evasion of the host organism [14]. Additionally, miRNAs have also been linked to immune function and are important because research has shown that in addition to their situational roles as oncogenes and tumor suppressor genes, specific miRNAs have displayed the ability to moderate the immune response of the host organism, effectively adding another point of control [15]. Croce's studies found the earliest evidence of miRNA in human cancer in 2002 after years of research [16,17]. About 1-5% of the human genome consists of miRNAs, and they are responsible for about 30% of the protein-coding genes in the human body. miRNA and siRNA are biochemically and functionally indistinguishable sub-classes of RNA and are identified based on their origin. The microRNA is derived from the double-stranded 60-70 nucleotide RNA hairpin precursor and siRNA from double-stranded RNA [8]. Insight into the Role of miRNAs in human cancer has made them particularly attractive tools and targets for novel therapeutic approaches. Functional studies have implicated Dysregulation of miRNA as a causal factor for many cancers [18]. As the Dysregulation of healthy genes is often linked to cancer, miRNAs have shown that they play a regulatory role in altering these processes [19]. The aforementioned let-7 family of miRNAs, initially discovered in *C. elegans*, is conserved throughout many vertebrates, including humans, and linked to cancer [8]. Oncogenic microRNAs called oncomiRs are implicated in the onset and maintenance of cancer when overexpressed. Antisense oligomers called antimiRs inhibit these oncomiRs. Upregulation and gain-of-function mutation of these OncomiRs and/or deletion or loss-of-function mutation of tumor suppressor miRNAs (TS-miRs) lead to cancer development [20].

Anti-miRs, or "antagomirs" as they are often called, are synthetically designed, target-specific oligonucleotide sequences that, when chemically modified and optimized for delivery, are potent inhibitors of miRNAs [21]. They can base pair in an antisense manner to the miRNA of interest, silencing its effect in the process and acting as a more specific "RNA sponge" that cancels out the effect of the miRNA [22]. Another method of regulating the effects of miRNAs is through the use of RNA zippers, which are small stretches of RNA that bind in a complementary fashion to two adjacent miRNA molecules binding them end-to-end and forming a DNA-RNA duplex. As noted in the research done by Meng et al., miR-221 and miR-17 were tested in the MDA-MB-231 and MCF-7 cell lines due to the relative expression levels and migratory properties of each [22]. Studies illustrated that each of the designed RNA zippers resulted in a significant knockdown of expression in each of the miRNAs used.

Additionally, the Let-7 family of miRNAs was utilized to measure zipper specificity because they are highly conserved. The result was that RNA zippers have very high target specificity and can distinguish between the conserved Let-7 family of miRNAs [22].

Mutant TP53 interferes with the Drosha processing machinery to inhibit mRNA processing and influences the process of oncogenesis [23]. Drosha and its partner DGCR8 (Di George syndrome critical region 8) are microprocessors essential for miRNA's biogenesis. Drosha and Dicer are required for miRNA maturation in sequential steps, and both belong to the RNAse III family [24].

Two fundamental inherent properties of miRNAs include homeostatic regulation of gene expression and energy for cellular responses [14]. Each tumor type has a distinct miRNA signature distinguishing it from normal tissues and other cancer types. This is a critical point to understand to incorporate the usage of miRNAs in clinical treatment for cancer [17]. In the past decade, it has been discovered that miRNAs can regulate cellular processes, indicating their involvement in cancer, and knowing both how different forms of cancer use them and also a few methods to biologically negate their effects will likely present physicians with novel treatment options for combating the ever-increasing prevalence of cancer within the United States [25,26]. In MM, many miRNAs acting together make it possible for the tumor to become invasive, and there are at least five dysregulated in this disease [27]. Based on the research, the five dysregulated examples are miR-744, miR-130a, miR-34a, let-7d, and let-7e, where all were found to be downregulated in MM and MGUS, they act as a tumor suppressor (TS-miRNA), and these can also serve as biomarkers for disease progression and response to therapy [27]. With these discoveries, nowadays, miRNAs have the potential to

serve as helpful tumor profiling tools. Studies have demonstrated that different forms of cancer have distinct miRNA expression signatures that allow for more efficient identification and control. As medical technology has continued to improve, it has become increasingly easier to sample large numbers of miRNA with ease. Furthermore, it was found that miRNAs can act as "prognostic markers by correlating miRNA expression with type-specific parameters such as metastatic potential, proliferative index, and response to existing treatments" [25].

It was conclusively decided that the ability to profile miRNA expression in a clinical setting would be essential and beneficial in determining a viable set of treatment options. Additionally, Hayes et al., found that microRNA expression signatures accurately identified tumors with an accuracy higher than 90%, possibly indicating that certain tumors associated with different forms of cancer contain their own set of weaknesses and points of regulation that could realistically be targeted by any of the previously mentioned methods of controlling miRNA expression [14]. The identification was based on 22 different tumors with the tissue of origin used as the basis of identification. OncomiRs can support the MGUS to MM transition, or TS-miRs can inhibit this transition. This information becomes a helpful tool when looking for an effective treatment option for MM. With the understanding of how certain miRNAs cause the growth and proliferation of different forms of cancer, and that miRNA profiling can be scientifically relied upon with a high level of accuracy, this review will aim to investigate the potential implications that miRNAs have on the Dysregulation of miRNA in MM, in addition to the key miRNAs that play a role in MM growth and progression.

Multiple Myeloma—Clinical manifestations, Clinical course, Staging and Role of Chemotherapeutic agents: Plasma cells develop from B lymphocytes (B cells), a type of white blood cell made in the bone marrow. Usually, when the body encounters bacteria or viruses, some of the B cells will change into plasma cells. Multiple Myeloma is a hematologic neoplastic disorder that results from the uncontrolled proliferation of malignant plasma cells, causing crowding of these cells in the bone marrow, leading to anemia and impairment of immunity. In addition, the malignant plasma cells produce M protein, which provides no immune benefit and accumulates in the body leading to renal failure and osteolytic lesions in the bone. MM accounts for approximately 10% of all hematologic cancers and still contains no cure [28].

Clinical Manifestations

Clinical presentation is usually due to hypercalcemia, osteolytic bone lesions leading to fractures, anemia, and renal failure. The common presenting signs and symptoms include bone pain, anemia, fatigue, pathological fractures, infections (mostly Pneumococcal), hypercalcemia, spinal cord compression (due to fractured vertebral body compressing the cord or from an extramedullary plasmacytoma), peripheral neuropathy, and signs and symptoms of renal failure. About 1/3rd of the patients' MM is diagnosed when being investigated for an unrelated condition. There are two premalignant stages of MM: monoclonal gammopathy of undetermined significance (MGUS) and Smoldering MM (SMM), an asymptomatic intermediate stage between a healthy cell and a malignant myeloma cancer cell. All the cases of MM are believed to be preceded by either MGUS or SMM stages. MGUS is characterized by a serum protein level of <3g/dL, less than 10% clonal plasma cells in the bone marrow, and an absence of Myeloma defining event. SMM is also an asymptomatic stage, with >3g/dL serum M-protein and/or 10-60% bone marrow Plasma cell infiltration with no- myeloma defining event [22,29]. MGUS stage is important when discussing the Role that miRNAs play in the biology of MM because many miRNAs are found to be decreased, and the expression of target genes, responsible for cell proliferation, apoptosis,

and DNA methylation, is increased [30,31]. There is a possibility of using targeted miRNAs at the stage of MGUS/SMM to prevent its progression to MM. MGUS is the most common form of plasma cell dyscrasia found in about 3% of the population above 50 years of age, and the prevalence increases with age. Therefore, there is a need for lifelong follow-up for patients with MGUS, as they develop MM at the rate of 1% per year. Patients with a Monoclonal spike in IgM or IgA had an increased risk of progression to disease when compared with patients with increased IgG [32]. Angiogenesis is a predominant and striking feature in MM and plays a significant role in the prognosis of the disease. SMM accounts for 15% of newly diagnosed MM. The risk of progression is substantially higher (about 10% per year) than MGUS, with approximately 3-4 years of progression [33].

Staging

Staging is often used to determine the progression of MM in different patients, the most common of which being the Durie-Salmon and International Staging Systems. The Durie-Salmon Staging System is older and determines the stage of MM using four measurements. The four measurements include the number of bone lesions, the level of calcium in the blood, the amount of hemoglobin, and the production rate of M-protein [34]. However, the Durie-Salmon Staging System has become less common with doctors as they are increasingly relying on other prognostic indicators.

MM can also be staged with the International Staging System (ISS). The MM Research Foundation reports that two blood tests can be determined: β2-microglobulin and albumin [34]. Albumin is an indicator of overall general health, and β2-microglobulin is a protein that indicates the extent of the disease. As these staging systems have limitations, a Revised International Staging System (RISS) was developed. It takes into account cytogenetic abnormalities and elements of tumor burden. Cytogenetic abnormalities determine the type, course, response to therapy, and disease prognosis. Among the cytogenetic abnormalities, the most common are: Gain(1q21), Del 17p, t(4,14), and t(14;16), which carry a high risk of progression to MM, trisomies plus any of the IgH translocations, t(11, 14) (q13, q32), t(6;14) (p21;q32), t (14, 20), (q32;q11) with a standard risk of progression and trisomies with an intermediate risk of progression. LDH and beta 2-microglobulin are other serum markers used in this classification [35]. An invasive and painful procedure, bone marrow biopsy has been the benchmark for diagnosing MM in patients. However, miRNAs are emerging as novel biomarkers for helping yield a prognosis for MM patients without a painful procedure.

Management

After risk stratification into a standard risk, intermediate and high-risk myeloma, the transplant eligibility of the patients is determined for autologous hematopoietic cell transplantation as it is associated with better patient outcomes compared with chemotherapy alone. Elderly patients, particularly those associated with organ dysfunction and poor performance status, are not usually considered eligible for transplant.

The patients are treated with different regimens based on the risk group. Generally, treatment is started with multiple chemotherapy agents, often referred to as induction therapy, followed by post-induction therapy with or without the transplant, and then maintenance therapy. The common drugs used in these regimens are Bortezomib, Lenalidomide, Cyclophosphamide, Dexamethasone (Dex), and Carfilzomib. After several cycles, a response to treatment and monitoring for relapse is made by the International Myeloma Working Group uniform response criteria for MM [36]. Today steroids such as Dex are essential for the treatment of MM. These steroids can be used alone or combined with other drugs to treat MM. Although it is essential to understand that steroids also suppress the immune system, increasing the risk of serious infections, these side effects usually go away after usage is terminated. For example, dexamethasone has been used for years to treat those eligible for transplantation [37]. Thalidomide, which was obsolete after its teratogenic effect causing phocomelia, came into light, became available for the treatment of MM to be used in combination with Dex, and is currently approved by the FDA for treatment of MM [38]. In a randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG), 202 patients were tested with Dex alone and used the combination of Thalidomide and Dex. Patients had a significantly higher response to the combination of Thalidomide and Dex compared with Dex alone [28,39]. Later on, Lenalidomide, an analog of Thalidomide, combined with Dex, was a better alternative to Thalidomide plus Dex and is currently a widely accepted therapy for elderly and frail patients with MM [10].

Bortezomib is a novel proteasome inhibitor currently approved to treat Myeloma in the relapsed setting after transplant or as a second-line treatment for patients not suitable for transplant. It acts by stabilizing the nuclear factor kappa B (NFκB). When combined with Dex, Bortezomib has a synergistic effect and significantly sensitizes myeloma cells to other therapeutic agents [40]. In combination with Dex, Lenalidomide was found to be more effective when compared to Bortezomib in combination with Dex with greater incremental quality-adjusted life years and cost-effectiveness in patients not eligible for transplantation [41]. Furthermore, the addition of Bortezomib to Lenalidomide and Dex improved progression-free survival and overall survival, which was statistically and clinically significant in pivotal the Phase 3 clinical trial [42]. Although Thalidomide, Lenalidomide, and Bortezomib are commonly used in combination with Dex to treat MM, the main challenges are relapse and resistance to therapy. MM still remains the second most diagnosed blood cancer in the world. With the increasing incidence and increased life span of MM patients, the burden of disease is ever- increasing, thus demanding a better understanding of molecular features of the disease that could result in better therapeutics. To that end, to better understand how miRNAs regulate MM pathobiology independently, we shift our attention to the relationship between the two and potentially explore the therapeutic potential of miRNAs to treat MM. Dysregulation of MicroRNAs in Multiple Myeloma miRNAs have been scientifically proven to play a significant role in maintaining human gene expression and controlling the proliferation and metastasis of an abundance of cancer types. Of specific relevance is MM, and to understand how various miRNAs are

expressed in this disease, one must first understand how the normal Role of miRNAs is altered in the case of MM, a process termed miRNA dysregulation. miRNA dysregulation in cancer was first reported in 2002, and the effects of miRNA on MM have been an ongoing investigation [14]. This unique property of miRNAs is important as we try to unravel how MM utilizes them to become cancerous because, in many types of cancer, tumor suppressor miRNAs that generally serve to protect against foreign control are negatively affected. According to Stamato et al., in the case of MM, tumor suppressor miRNAs that generally serve a positive role in the human body become "hijacked," and the body loses its ability to defend against cancer cells [43]. A specific example of tumor suppressor miRNA in the human body, miR-29b, is downregulated in MM tissues and cell lines [44].

Restoration of miR-29b induced apoptosis *in vitro* and exerts anti-tumor activity *in vivo* via downregulating FOXP1 [44], sp1, MCL1, and CDK6 [45]. miR-29b demethylates and upregulates SOCS1, which is often silenced by promoter hypermethylation in MM, thereby negatively regulating IL6-STAT3 signaling [46]. This Dysregulation of a normally functioning miRNA is just one example of how the disease effectively overpowers the defense mechanisms of the host cell. Upregulation of miR-196b-5p and downregulation of miR-99a-5p resulted in the inhibition of apoptosis of myeloma cells via the TGF-β/Smad signaling pathway [47]. Serine/threonine kinase PDPK1 and its substrate RPS6KA3 are overexpressed in MM, which was linked to a significant decrease in miR-375 [48]. miR-137 has been identified as TS-miR in MM, suppressing tumorigenicity by targeting the anti-apoptotic gene *MCL1* [49]. In addition, ectopic expression of miR-137 inhibits AKT phosphorylation and improves the Dex sensitivity by targeting MITF, a key transcription factor in MM development and progression [50]. In another study, restoring miR-137 in bortezomib-resistant MM cells resensitized the cells via downregulating *AURKA* and ATM/Chk2 and increasing the expression of p53 [51]. Other TS-miR, miR-27a, is downregulated in bortezomib-resistant MM cells, and ectopic expression increased the sensitivity of MM cells by targeting CDK5 [52].

Several studies confirm the tumor-suppressive Role of miR-125b in MM [53-55]. Jiang et al. reported for the first time that miR-125b might function as oncomiR by targeting a tumor suppressor gene, MKK7 [56]. Another example of Dysregulation that occurs in the case of MM is that of Cyclin D2, a protein that is heavily involved in the cell cycle, which illustrates the multifaceted nature of the disease and the varied symptoms that are often experienced as a result [57]. Downregulation of miR-15a, miR-19a, miR-19b, miR-20a, miR-196b and miR-320 which directly target Cyclin D2 could contribute to overexpression Cyclin D2 in

MM [58]. In another case, Argonaute 2, which is involved in the biogenesis pathway of miRNAs and the subsequent degradation of mRNA transcripts, has also been shown to result in the metastasis and proliferation of MM cells [59]. Multiple miRNAs can act on one gene, and one miRNA can act on multiple genes. Thus, interfering in single miRNA may not produce desirable results. Also, the miRNA has to be injected in the blood and is subject to rapid degradation by the nucleases in the blood [60].

MicroRNAs in MGUS to Multiple Myeloma

According to Picchiori et al., a set of miRNAs has been identified that serve as blood serum biomarkers to identify examples of miRNA dysregulation at the MGUS stage of the disease. They used real-time PCR to profile miRNA expressed in MM cell lines. Compared to healthy plasma cell lines, 41 miRNAs were upregulated, and seven were downregulated in MGUS cell lines. miR-21 was found to be upregulated more frequently, which is also upregulated along with miR-181a, miR 106b ~ 25, miR 93, miR-106b, and miR-25 in MM and MGUS samples [61]. These upregulated miRNAs might play an early role in developing mutated clonal plasma cells in MGUS, and targeting therapy against them might prevent progression to MM [62]. miR-21 is of special interest since it is found to be upregulated in many cancers. STAT3 upregulates the gene encoding miR-21 by inhibiting apoptosis of myeloma cells without IL-6 [63].

MicroRNAs involved in malignant transformation of MGUS to MM

The miR-32 and miR-17 cluster 92 were upregulated in MM but not in MGUS or healthy plasma cells. miR-19a and -19b are part of miR-17~92 target SOCS-1. SOCS-1 plays a critical role in negatively regulating cytokine pathways, including IL-6 and JAK/STAT pathways. SOCS-1 is frequently silenced by methylation in MM, and the miR -17~ 92 clusters targeted the proapoptotic regulator BIM in MM cells, leading to their enhanced survival [61]. These miRNAs can be a potential target, and the progression from MGUS to MM might be controlled by targeting antimiRs towards these pathways. Known miRNAs and their relationship with progressing stages of the disease from healthy tissue to fully progressed symptomatic multiple Myeloma has been depicted in Figure 2.

Key MicroRNAs that Play in MM Growth and Progression

A normal human plasma cell differentiation involves about 63 miRNAs which regulate several critical pathways [61]. Research has found that in most MM cases, miRNAs are more commonly upregulated than downregulated, indicating that in this type of cancer, miRNAs have a more prevalent role as functional oncogenes (oncomiRs) than they do as inactivated tumor suppressor miRNAs. Their functional role, whether it be upregulatory or downregulatory, is critically important, as synthetically designed antagomirs could be used to silence oncomiRS or upregulate any silenced tumor suppressor miRNAs to offset the cancer effects. One key miRNA that is of paramount importance is miR-20a, which has been shown to play a role in the proliferation of MM by exhibiting control over the PTEN/PI3K/AKT cell signaling pathway [64]. The completed research showed that there was a significant decrease in the expression of PTEN at the gene and protein levels but that the subsequently overexpressed miR-20a in MM patients used PTEN as a target gene, effectively causing the expression of the gene to be silenced in the process. Furthermore, when a miR-20a inhibitor was employed, the result was decreased migratory ability and proliferation in MM cells and a pronounced decrease in the levels of PTEN expression. As more research is done on miR-20a, this subject presents a potential option in the treatment of MM [64]. A set of miRNAs were also identified for MM patients using bone

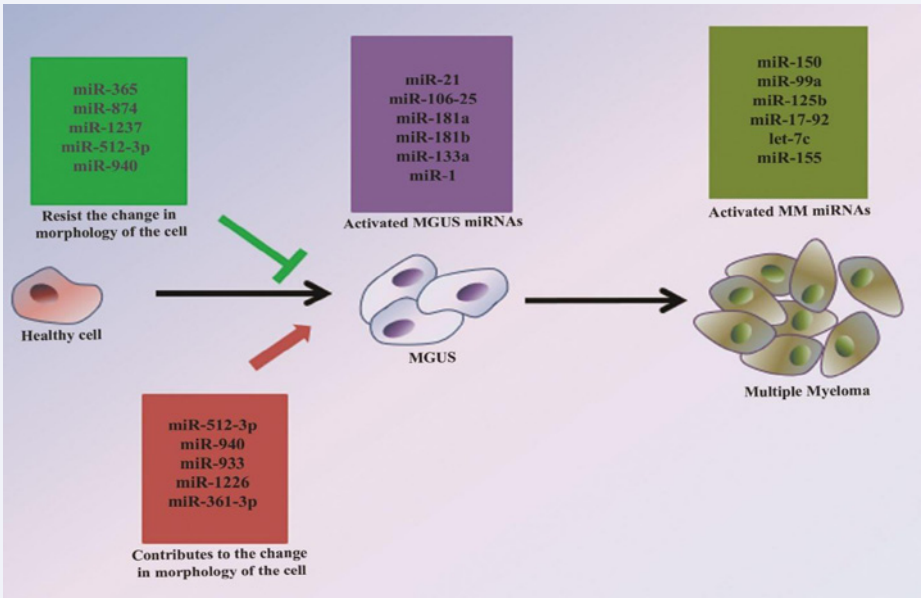

Figure 2 A model depicting the relationship of known miRNAs and their relationship with progressing stages of the disease from healthy tissue to fully progressed symptomatic Multiple Myeloma.

marrow tissue, including miR-32, miR-21, and miR-17-92 [61]. miR-125b (oncomiR) and miR-34a (TS- miR) can be negative or positive regulators of the wild-type P53 gene in MM [65]. It is noteworthy that the expression of these miRNAs is unique to the malignant myeloma stage of the disease, adding another promising factor of control as more information is uncovered. Studies also showed that miR-720, miR-1308, and miR-1246, when tested in conjunction with one another as myeloma biomarkers in blood serum, could distinguish between healthy patients, affected patients at the asymptomatic MGUS stage, and those with the fully progressed MM stages of the disease [60,66]. Although the exact mechanism for each hasn't been experimentally determined, many miRNAs have been shown to play a role in MM. As the list grows and more details about how MM uses miRNAs come to light, treatments will likely target oncogenic miRNAs needed for the disease to function.

Delivery of MicroRNAs through Nanoparticles

In recent times, nanoparticles have gained substantial attraction as a promising novel tool to deliver miRNA to their desired tumor site and counter tumor progression. The paramount goal of targeted delivery systems is to transport therapeutic agents to their respective tumor sites to decrease anti-cancer drugs/agents [67]. To produce an effective nanoparticle-mediated delivery system, the most effective characteristics to possess are stability, high nanoparticle volume, and versatility in carrying various forms of therapeutic agents [68]. Magnetic nanoparticles (MNPs) have risen as a promising type of nanocarrier that has favorable implications on chemotherapeutics. In the presence of magnetic fields, magnetic nanoparticles flourish in their delivery abilities in delivering chemotherapeutic agents in a stable and protected manner [67].

On the other hand, independent chemotherapeutic agents without the aid of MNPs have shown derivative effects, such as toxicity, on healthy tissues and organs as they lack the target intuition that nanoparticles possess [68]. Therefore, miRNA conjugated nanoparticle systems have risen as a more effective alternative to naked miRNA circulation due to the lack of stability and short half-life [68]. More precisely, studies by Yu et.al; reveal [69] that via the use of PEI-modified MNPs then conjugated with miR-145, miR-21, and miR- 9. Furthermore, their studies showed that in mice with tumors treated with these MNPs, the weight and volume of their tumors reduced down to 58% compared to that of the control groups. Autophagy is an evolutionary conserved physiological process with a fundamental role in the developing, differentiation, and survival of eukaryotic cells [70]. In many instances, autophagy directly yields cancer cell proliferation because it allows cancer cells to avoid apoptosis. While MNPs may be profoundly effective for tumor suppression and autophagy regulation, other varieties of nanoparticles exist with similar capabilities. Lipid- based nanoparticles have become a notable candidate when discussing effective drug delivery and targeting. More specifically, solid lipid nanoparticles (SLNPs) have the innate ability to deter miRNA degradation during systemic circulation. When tested through a system built to target a cancerous lung for CSC therapy, the combinations composed of miR-34a-SLNPs effectively inhibited any further tumor development *in vivo*. Other forms of lipid-based nanoparticles, like LPH, can enhance/ activate therapeutic activity in melanoma cells by disabling the MAPK pathway. Polymeric nanoparticles also present promising results for effective delivery. When conjugated with tumor-targeting ligands, specific polymeric nanoparticles, like amine-terminated polyamidoamines (PAMAMs), exhibit lower toxicity and higher tissue penetration [30]. An experiment by Wang et al. presented a conjugation of an S6 aptamer dendrimer encapsulating miR-34a, forming lung cancer-targeting delivery systems [71]. This conjugation could inhibit cell proliferation, migration, and invasion, proving its efficacy as a therapeutic agent that targets autophagy- related mechanisms and deters cancer growth. Other note-worthy nanoparticles delivering miRNA are pH sensitive and biocompatible polyamines [70]. Their ability to release therapeutic miRNA and inhibit polyamine metabolism makes them valuable assets for efficient delivery. Biopolymer-based nanoparticles are another variation of drug delivery that has been heavily utilized. Copious studies and experiments reveal hyaluronic acid- chitosan nanoparticles (HA-CS) as an ideal biopolymer carrier for systemic drug delivery. By restoring original miR-34a levels, the HA-CS nano-complexes delivering doxorubicin (DOX) and miR-34a enhanced antitumor effects of DOX *in vivo* and *in vitro*. Moreover, the delivery of miR-34a inhibited cancer cell migration [70]. In another study, codelivery of miR-34a and Smac synergistically improved the anti-tumoral efficacy [72]. This result highlights the potential in a codelivery of chemotherapeutic agents and tumor suppressor miR-34a as a strategy for antitumor therapy.

While the miRNA conjugated nanoparticles promise many promising prospects, there are implications in the clinical setting, including circumventing the risks associated with the use of nanoparticles and nanotechnology as a drug delivery tool in modern-day medicine. To achieve ideal goals, the carrier system should protect the therapeutic agent (the drug) from the circulatory nucleases and deliver it to the target site intact [67]. However, the caveat to initiating the use of nanoparticles in practical clinical settings is that the development of oral delivery vehicles is necessary to push nanoparticles through clinical development [67].

miR-34a-loaded nanoparticles have shown great potential in tumor inhibition in SCID mice [73]. Di Martino et al. explored the anti-cancer activity of miR-34a mimics encapsulated in stable nucleic acid-lipid particles (SNALPs) against multiple myeloma xenografts in SCID mice [74]. They observed significant tumor growth inhibition without systemic toxicity, indicating survival benefits. In another study, the therapeutic potential of miR-34a was also investigated in subcutaneous and orthotopic human multiple myeloma xenografts in NOD-SCID mice, where miR-34a was delivered systemically using a 160 nm-lipid- based nanoparticle that contains a miR-34a mimics [73]. The tumors from mice treated with miR-34a-chitosan/PLGA nanoparticles were significantly smaller than the control group, evidencing possible therapeutic efficacy [73]. Furthermore, it was observed that i.p., delivery of the mixture of miR-30a/b/c/d/e (miR-30mix) using lipid N.P.s decreased tumor burden and increased survival in a murine xenograft model of human MM [75]. In another study, Zhao et al. examined tumor growth in mice after i.p. delivery of antisense-miR-221-222 using N.P.s in combination with Dex [76]. Survival was increased, and tumor burden was decreased in mice

treated with antisense-miR-221-222-NP compared to the control group. However, the therapeutic efficacy of miRNA-loaded nanoparticles is challenged by their low encapsulation efficiency, primarily due to the hydrophilic nature of miRNAs [68]. In conclusion, miRNA-loaded nanoparticles/nanoplexes serve multifaceted purposes in the pathogenesis of various forms of cancer, including Multiple Myeloma. Although challenges remain in the toxicity and cell-specific delivery mechanisms of miRNA-loaded nanoparticles, studies have shown that nanoparticles supplemented with antibodies and/or ligands ensure miRNA delivery to cell-specific areas [69]. However, clinical applications must be further explored to ensure miRNA-loaded nanoparticles as a sustainable and promising therapeutic method in MM and other forms of cancer.

Relate the efficacy and promise of miRNA used as therapeutics in treating MM to the COVID-19 vaccine

The applications of miRNA-based therapeutics and prognostic/diagnostic tools are not simply limited to MM. MiRNA has been examined as a potential tool in combating the novel coronavirus in the midst of the current 2020 pandemic. It has recently been hypothesized that using synthetic miRNA would allow for the inhibition of COVID-19 mRNA molecules, which would significantly hinder the progression of the infection. More specifically, El-Nabi et al. hypothesized that the use of synthetic miRNA molecules which target the 3' UTR and ORF9 regions could, in theory, effectively reduce or completely disable the process of viral particle assembly by inhibiting translation of the mRNA by ribosomes, which would, in turn, prevent the spread of viral particles [77]. Viruses can utilize host cells to translate nucleic acids into protein complexes. Taking advantage of miRNA, which controls 65% of protein synthesis in animal cells via post-transcriptional adjustments to mRNA, would be beneficial in clinical practice. MicroRNA based technologies could reveal themselves as a new method of combating viruses such as the novel coronavirus. Additionally, it has been identified that viruses also utilize miRNA to control certain cell functions by preventing translation or degrading the mRNAs expressed by the host cell. In this light, it is simple to see that by finding methods to inhibit these miRNAs, the effectiveness of the viral infection may be decreased as well. On top of all of these different applications to viral infections, miRNAs can also be seen as potential markers for early diagnosis, prognosis, and prediction of response to various types of therapy in diseases that either downregulate or upregulate the concentrations of certain miRNA molecules [78]. Furthermore, according to Bhatti et al., miR-5197-3p has recently been identified as the most valuable site for interaction with SARS-CoV-2, and complete complementary miRNA regions in the viral genome have been predicted. The proposed site lacks competition, making it ideal for a synthetic miRNA to bind. Therefore, it could effectively slow or halt virus pathogenesis [79]. Because both viruses and host cells use miRNA in the case of SARS-CoV-2, further research into miRNAs as therapeutics and biomarkers could be vastly beneficial when there is a need for novel COVID-19 therapeutics. Another suggestion for such therapeutics made by Chauhan et al. indicates that if miRNAs were arranged to target both ACE2 and TMPRSS2 receptors and the viral RNA, it could negate and minimize viral replication. More specifically, it was proposed that host miR-27b regulate ACE2 while viral miR-147-3p regulates TMPRSS2 receptors.

However, it should be noted that there is still a necessity for extensive research regarding miRNA as both a therapeutic agent and biomarker. While miRNAs as therapeutics have been reviewed and documented for their key roles and recent advances in some cancers and other diseases, the research still needs to be conducted in virology. There are also additional concerns about the viability of miRNA therapeutics due to offsite toxicity and the potentially unstable nature of miRNA. Various nanoparticles/nanocarriers have been suggested to combat the poor miRNA loading efficacy, off-target toxicity, and immunogenicity that has been getting in the way of potential miRNA therapeutics [80]. Similarly, Mishra et al. has also revealed that miRNAs could be a therapeutic target and biomarker for COVID-19 severity. Furthermore, they suggested that miRNA could improve the immune system's effectiveness and decrease the risk of infection via the regulation of immune cells using miRNA [81]. Though research is still required, it is notable that Demirci et al. conducted a computational analysis regarding miRNA in COVID and possible genetic precursors of miRNA. In their analysis, they extracted 950 hairpin structured sequences from the SARS-CoV-2 genome and 29 miRNA precursor regions found in the novel coronavirus genome. Furthermore, targeting analysis showed that 30 viral mature miRNA-like sequences could target 1367 human genes, many of which had vital roles in cellular processes. However, it should be noted that it remains ambiguous whether RNA-based viruses are capable of miRNA production. While DNA-based viruses have been noted to be capable of miRNA production, RNA-based viruses such as SARS- CoV-2 can do so. The reason this remains a complicated issue is that RNA viruses that replicate in the cytoplasm don't have access to nuclear miRNA machinery, and since RNA is the genetic material, miRNA may interfere with viral replication as well. Additionally, Demirci et al. were also able to conclude that among the 2654 human miRNAs analyzed, 479 of them would be capable of targeting SARS-CoV-2 genes. It should also be noted that it may be beneficial to develop antagomiRs to combat viral miRNA sequences. This would combat the potential existence of viral miRNA in SARS-CoV-2, which may inhibit cellular function and enhance virus replication [82]. Additionally, a loss of miR-197-5p-mediated defense against SARS-CoV-2 may directly correlate to an increased mortality rate in patient groups with cardiovascular disease. Some mutations, such as the C3037U mutation, play a significant role in the transmission. When the C3037U and A23403G mutations are linked, viral infectivity may be enhanced via structural changes in the S protein [83]. This study provides more background about tracking the linkage of the C3037U and A23403G sites; however, further studies into the associations between miR-197-5p expression, the C3037U mutation, and the seriousness of COVID-19 disease in these cardiovascular patients are required. Even with copious research, no study can thoroughly explain whether miRNA acts as gene regulatory elements when targeting viral transcriptions or act as the host's defense against viral infection. But a checkpoint for further attenuation of live vaccines is the prospect of using host miRNA binding sites in the live-attenuated virus genome. For instance, the discovery of miRNA target sites in viral pathogens

opens up doors that can create specific viral vaccines targeting certain cells or species.

CONCLUSION

After an overview of structural miRNA information and their functional role in MM, this review delves deeper into discussing the details of how miRNA is dysregulated in MM. Downregulation of tumor suppressor miRNA and upregulation of oncomiRs are mainly responsible for the proliferation and metastasis of malignant plasma cells in MM. An example of miRNA dysregulation is miR-29b, losing its ability to act as a tumor suppressor, and thus the body loses its ability to defend against the spread of MM. This Dysregulation is a variable process that is differentially expressed throughout the body due to the many miRNAs involved in the process and the fact that the mechanisms are not all identical. In addition, MM is challenging to treat due to relapse, drug resistance, and various mutations occurring in different genes. While much information about miRNAs has been put on display in the past decade, synthetically designed miRNAs (antimiRs) to combat MM is still a novel process that is not well defined. Many miRNAs are directly affected in MM (Table 1), yet an answer to "how" many of them work remains unclear. According to Morelli et al., one method for blocking the effects of miRNAs is via the use of locked nucleic acid antisense oligonucleotides (LNA- ASO), which were shown to downregulate the expression of the oncogenic miR-17-92 family. This recently published research has shown conclusively that the growth of miRNAs within this family can be halted, indicating that there is hope for controlling MM progression at the nuclear level [84]. Additional research with LNA-ASOs, as they are aptly termed, has shown that they can also control levels of LDL cholesterol circulating within the bloodstream, indicating that there may be a variety of ways to employ these oligonucleotides to target oncogenic miRNAs [85]. Because MM is blood cancer and is, as a result, expressed throughout the entire body, synthetically designed oligonucleotides could theoretically be more easily designed to target the disease. Traditional drug treatments like Thalidomide, Dex, and Lenalidomide are heavily used but are not a permanent cure for Myeloma. Additionally,

Table 1: [Different tumor-suppressor microRNAs (TS-miRNAs) and oncogenic microRNAs (Onco-miRNAs) in multiple Myeloma].

miRNA	Regulation	Location	Targets	References
miR-137/197	Down	1p22	AURKA, p-ATM/Chk2, MITF, MCL-1	[49-51, 88]
miR-34a	Down	1p36.22	Bcl-2, Cyclin D1, SIRT1, VEGF, CDK4/6, p53, $p27^{KIP1}$, Survivin and Notch1	[27, 72-74]
miR-27a	Down	19p13.12	CDK5	[52]
miR-29b	Down	7q3b	MMP2, HDAC4, SP1, MCL-1, CDK6, STAT3, DNMT3A, JUN, DNMT3B, c- FOS, PSME4, MAPK	[45, 89-92]
miR-125b-5p	Down	11q24.1/21q21.1	IRF4, MALAT1	[53, 55, 86]
miR-15a/16	Down	13q14.3	CABIN1, AKT3, VEGF, rp-S6, MAPK	[93, 94]
miR-30-5p	Down	6q13	Wnt, β-catenin, BCL9	[75]
miR-92a	Down	13q31-q32	RPL7A, MCL-1, CDK9, BCL2L11	[95, 96]
miR-33b	Down	17p11.2	PIM1	[97, 98]
miR-199a-5p	Down		DDR1, HIF-1α	[99]
miR-320	Down	Chr.8: 22244966	Cyclin D2	[58]
miR-214	Down	1q24.3	PSMD10	[100]
miR-203	Down	14q32-33	Bmi-1	[101]
miR-130a	Down	11q12		[27]
miR-22	Down	17p13.3	LIG3	[102]
miR-135b	Down	1q32.1	Cyclin D2	[58]

Table 2: Clinical trials involving MicroRNAs for the treatment of Multiple Myeloma.

STUDY TITLE	STATUS	CONDITIONS
Identification of Hematological Malignancies and Therapy Prediction Using microRNAs as a Diagnostic Tool	Not yet recruiting	Lymphoma, B-Cell Follicular Lymphoma Hodgkin Lymphoma Multiple Myeloma
A Multicenter Phase I Study of MRX34, MicroRNA miR-RX34 Liposomal Injection	Terminated (5 immune-related serious adverse reactions)	Primary Liver Cancer SCLC Lymphoma Melanoma Multiple Myeloma Renal Cell Carcinoma NSCLC
The Molecular Characterization of Multiple Myeloma at Relapse	Completed	Multiple Myeloma
Pharmacogenomic Study in Myeloma Patients Treated with Melphalan-prednisone-thalidomide or Lenalidomide-dexamethasone	Unknown	Myeloma
Carfilzomib, Cyclophosphamide and Dexamethasone in Newly Diagnosed Multiple Myeloma Patients	Active, not recruiting	Multiple Myeloma

like the International Staging System, the current standard is not as accurate as researchers hope it could be. Furthermore, there has been a lack of research regarding the expression and deregulation of miRNA in MM to supplement the development of new potential therapies or staging methods based on miRNA [86,87]. However, a wave of new research regarding the changes in miRNA concentration during MM has allowed for a greater understanding of the pathobiology regarding MM both before and during stages of malignancy, which has opened the doors to further research [86]. Thus, this review hopes the analysis of the different upregulated and downregulated miRNA clarifies the ability to use miRNA as an accurate method of staging MM. Based on the information mentioned above on the disease, the most effective short- term method of controlling the disease is to prevent progression from the asymptomatic MGUS stage to the malignant myeloma stage. Unfortunately, many of the miRNAs that have been shown to inhibit the progression of the disease still require more testing before these new drugs will be cleared for use in human clinical trials (Table 2). The ultimate goal of this review is to uncover the successful attempts in modern medicine to use miRNAs to combat cancer, specifically MM, and to highlight the shortcomings as well, thus forging a clear path to a change that could potentially revolutionize the field of oncology/hematology.

AUTHORS' CONTRIBUTIONS

Conceptualizatio- SKB, S.B., and S.K. Literature search- K.V., AM, I.H., S.A., S.S., and YDM. Original draft- K.V., AM, and I.H. Review and Editing, I.H., SKB, S.B., and M.Q. Supervision, SKB, S.B. and S.K., Funding Acquisition, SK, M.Q., S.B., and SKB. All authors revised the manuscript and approved its content.

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