Review

MiR-622 Expression and Role in Multiple Tumors

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Abstract

Worldwide, cancer causes a lot of suffering and death. Both surgical and nonsurgical methods are used in modern cancer therapy. The most recent development is molecularly targeted treatment. MicroRNAs (miRNAs) are a class of short, non-coding RNAs that may be found in plants and animals and play an important role in cancer and other disorders by modulating a wide range of cellular and organismal functions. It has been revealed that the miRNA miR-622 regulates many pathways that have an impact on illness. Tumors including glioma, as well as those of the liver, colon, and breast, may benefit or suffer from aberrant miR-622 expression. In this article, we outlined the processes and linked molecules of miR-622 and analyzed its expression levels and clinical consequences in different types of cancers.

Keywords: Cancer, microRNAs, mechanisms, and molecules; specifically, miR-622

1. Introduction

Regardless of where one lives or one's economic status, cancer is the top cause of mortality. From 2008 to 2030, the global cancer burden is projected to rise by 100% in low- and middle-income countries [1]. Early identification and treatment are crucial for improved health management and effective cancer screening. For example, mutations in genes in the EGFR signaling pathway may be a negative predictor of anti-EGFR monoclonal antibody therapeutic efficacy in colorectal cancer (CRC) [2]. In addition, the most widely used biomarkers for detecting gastric cancer are carcinoembryonic antigen (CEA) and Glucoprotein antigen 199 (CA19-9). Treatment options for cancer nowadays range from surgery and radiation to hormone and targeted therapies [4]. Breast cancer, leukemia, and colorectal cancer have all been successfully treated using molecular targeted treatment. Many additional cancers, such as lung cancer and ovarian cancer, have shown promising clinical results [5]. In order to effectively diagnose and treat cancer, research into molecular markers and molecularly targeted therapies is crucial.

MicroRNAs (miRNAs) are a kind of tiny noncoding RNA found in the genomes of almost all eukaryotic organisms [6]. MicroRNAs (miRNAs) control how much a gene is expressed by interfering with transcription, translation, or epigenetic processes based on the recognition of homologous sequences [7]. Inhibiting transcription by complementary base pairing with target mRNA, miRNAs regulate the expression of several downstream target genes [8, 9]. Disease progression is affected by miRNAs in several ways [10], [11], including cell proliferation, cell death, the immunological response, and the manufacture of neurotransmitters. In addition, new research investigating miRNAs' roles in malignancies have shown that aberrant miRNA expression is a common feature of the disease. For example, miR-106b-5p increases breast cancer lung metastasis via modulating the Rho/ROCK1 pathway [12]. Several types of cancer have miR-146a-5p as a potential noninvasive biomarker and therapeutic target [13]. More research is needed to completely elucidate the roles of miRNAs in the development of various malignancies. There is mounting evidence that the

microRNA miR-622 plays a role in cancer progression or suppression in a wide variety of malignancies, including breast, glioma, CRC, HCC, lung, gastric, melanoma, ovarian, prostatic, and pancreatic cancers [14, 15], 16], 17], 18], 19», 20», 21», 22», 23]. MiR-622 regulates molecular pathways such as EGF/ERK signaling and K-Ras signaling, and its expression is linked to the clinical characteristics of these cancers [17], [18], [19], [24], [25]. miR-622 is a possible target for the treatment of cancer and is linked to medication resistance [26]. In addition, miR-622 may affect other disorders by, for instance, binding to circ_ANRIL in cerebral ischemia-reperfusion to regulate the NF-kappaB pathway and reducing vascular endothelial damage due to oxygen-glucose deprivation and reoxygenation [27]. In this review, we compile information on miR-622's expression in malignancies and its effect on tumor characteristics, oncogenes, and anti-oncogenes. The potential of miR-622 as a biomarker in a number of tumors is discussed, along with its biological activities, target genes, and interacting molecules.

2. Methods for a Search

To do this, we queried PubMed for papers published as recently as April 2011. MicroRNA-622, miR-622, and cancer are some related terms. Titles and abstracts were used to identify articles that were relevant to this review's subject. Literature, case reports, meeting minutes, correspondence, publications whose entire text is unavailable, retractions, and revisions that are not related to the topic at hand should be disregarded. Finally, the two writers conduct their own, separate analyses of the complete texts of the chosen scholarly works.

4.1. HCC

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the two most common histological subtypes of primary liver cancer, both of which are etiologically and physiologically diverse [29, 30]. It has been observed that miR-622 expression is dramatically downregulated in HCC tissues and cells. MiR-622 has been shown to induce cell apoptosis [17] and suppress cell growth and invasion. The proliferation and migratory abilities of HCC cells are greatly aided by miR-622 inhibition [31]. Serum HBsAg positivity, cirrhosis, tumor stage, vascular invasion, and intrahepatic metastases were all linked with low miR-622 expression [24]. According to Kaplan-Meier analysis, patients whose miR-622 levels were low had a lower median overall survival time compared to those whose miR-622 levels were high. MiR-622 expression was shown to be an independent survival predictor for patients with HCC in a multivariate survival study [24]. Furthermore, as shown by Dietrich [25] and Gaza [32], miR-622 is linked to sorafenib resistance.

4.2. Glioma

Most malignant tumors found within the skull are gliomas [33]. Half of all gliomas are glioblastoma, a highly invasive kind [34]. MiR-622 is known to be severely downregulated in glioma tissues and cell lines, according to a plethora of research. Increased expression of miR-622 inhibits glioma cell invasion and migration, according to functional studies [35]. Furthermore, miR-622 promotes cell cycle arrest in the G0/G1 phase in glioma cells and suppresses cell growth [15]. Downregulation of miR-622 was substantially connected with advanced pathological grades and poor Karnofsky scores in a study examining the association between miR-622 and the clinical characteristics of glioma. Kaplan-Meier analysis demonstrated that decreased miR-622 expression is strongly linked to poor overall survival. Downregulation of miR-622 was shown to be an independent indication of poor prognosis in glioma patients using Cox regression analysis [36]. Overexpression of miR-622 suppresses tumor cell proliferation, migration, and invasion in glioblastoma [37]. miR-622 expression is low in glioblastoma tumor tissues and cells.

4.3. CRC

CRC is a contemporary illness that kills around 700,000 people a year [38]. MiR-622 levels in CRC are often found to be much lower than those in normal tissues or cell lines. The miR-622 level was observed to be decreased in metastatic

CRC tissues compared to nonmetastatic CRC tissues. Furthermore, miR-622 was shown to influence tumor growth and migration in a functional study [39]. Experiments in both vitro and in vivo have shown that miR-622 may act as an angiogenesis inhibitor by reducing cell proliferation, migration, and tumor development [16]. In contrast, another study reported that miR-622 expression was elevated in CRC tissues and cell lines, and that downregulating miR-622 expression reduced cell motility and invasion [40].

Surgery, in conjunction with adjuvant chemotherapy, radiation, and immunotherapy, is the gold standard for treating CRC [41]. Increased success in developing tailored drugs may potentially help CRC patients live longer [42]. Recent studies have shown that miR-622 is upregulated in CRC cells exposed to ionizing radiation, leading to radioresistance [43]. There has also been research into the mechanisms of miR-622 in relation to sevoflurane medication [44].

4.4. GC

Gastric cancer is the fifth most prevalent form of the illness overall [45], although it is also one of the most diverse. In GC cells and tissues, miR-622 expression was shown to be rather low. Regulation of invasion, migration, tumorigenesis, and metastasis by miR-622 is linked to cell differentiation and lymphatic metastasis [19]. Another study confirmed that miR-622 inhibited cell invasion by lowering levels of Laminin gamma-2 subunit (LAMC2) [46]. Thus, miR-622 acts as a tumor suppressor in GC and may be a therapeutic target for GC that has spread.

4.5. Carcinoma of the Breast

In addition to being the largest cause of cancer-related mortality among women, breast cancer is the most common malignancy globally. Individuals in industrialized nations account for half of all breast cancer cases [47]. Patients with breast cancer had lower levels of miR-622 in their plasma and tissues [14]. The ability of breast cancer cells to migrate and invade, as well as higher grades, are all linked to low miR-622 expression [14]. Overexpression of miR-622 is linked to poor prognosis, tumor mesenchymal transition, cell viability, and invasion, according to a database bioinformatics analysis and in vitro experiment-based research [48]. More research is needed on miR-622's expression and roles.

In Mojdeh Mahmoudian and colleagues' study, it was discovered that certain microRNAs showed increased expression in BC tumor compared to the adjacent tissues. Specifically, hsa-miR-25-3p, -29a-5p, -105-3p, and -181b1-5p were upregulated, while hsa-miR-335-5p and -339-5p were downregulated. The upregulation or downregulation of these candidate microRNAs was found to be associated with TNM stages, except for hsa-miR-339-5p. Additionally, with the exception of hsa-miR-105-3p, each candidate microRNA correlated with HER-2 status. Furthermore, the analysis of ROC curves revealed that the combination of these six microRNAs could potentially serve as a biomarker to differentiate between tumor and non-tumor breast tissue samples.

4.6. Melanoma

Melanoma is a primary cause of cancer-related mortality and has the potential to spread [49]. For this reason, precise melanoma staging is essential. When comparing primary and metastatic tumors, miR-622 expression was shown to be considerably downregulated in melanoma tissues and cells. miR-622 is related with disease-specific survival outcomes, according to a study of The Cancer Genome Atlas (TCGA) database [50]. MiR-622 has been linked to both cell proliferation and angiogenesis [20], according to another research.

4.7. Variant cancers

Cholangiocarcinoma (CCA) tissues and cell lines have been discovered to have reduced levels of the microRNA miR-622. miR-622 expression may influence cell proliferation, migration, and invasion and is related with T stage and lymph node metastases [18], [51]. The expression of miR-622 is downregulated in lung cancer [52], and it regulates cell migration and invasion, epithelial-mesenchymal transition, and tumor metastasis. Concerning therapy, miR-622 has

been shown to be an independent predictive biomarker for the response of patients with high-grade serous ovarian cancer (HGSOC) to platinum-based chemotherapy [21]. In addition, miR-622 overexpression is related with lower patient survival outcomes following platinum treatment in BRCA1-mutant ovarian cancer [53]. In esophageal squamous cell carcinoma (ESCC), miR-622 also has a tumor-suppressive function. miR-622 is correlated with tumor subtype, tumor size, invasion depth, TNM stage, and lymph node metastasis, making it an independent risk factor for ESCC prognosis. Also, miR-622's function is linked to cell division, cell death, metastasis, and invasion [54]. Similar miR-622 functions and an association with RCC metastasis [55] have been identified in renal cell carcinoma (RCC). Both prostate [22] and pancreatic [23] cancers have been linked to reduced miR-622 expression.

5. MiR-622's role and associated mechanism in tumorigenesis.

It is widely known that miRNAs detect target mRNAs via complementary base pairing to limit protein production [56], [57]. We described the role of miR-622 in tumor regulation and the associated signaling pathways to better comprehend its impact on malignancies. In addition, Fig. displays the functions of miR-622 in HCC and the ways by which it does so. 2.

5.1. Cell division and cell death

The continual expansion and evasion of cell death characteristic of tumors necessitates a cascade of abnormalities [58]. Reduced miR-622 expression in CCA cells increases cell proliferation by modulating c-Myc expression directly [51]. To increase MAPK1 mRNA expression, stimulate proliferation, and suppress apoptosis in HCC, hsa_circ_0101432 can target miR-622 [17]. Researchers have shown that miR-622 has anticancer effects via reducing phosphorylation of JNK and NF-B [24], which in turn inhibits JNK and NF-B signaling. Targeting K-Ras [50] or interacting with circ_0119872 to control the target gene G3BP1 and downstream Wnt/-catenin and mTOR signaling pathways [20] are two methods in which miR-622 suppresses clonogenicity and proliferation in melanoma. In a similar vein, miR-622 may restrain the growth of CRC cells by lowering their expression of K-Ras [39]. Intriguingly, Sev administration controls hsa_circ_0000231 expression while simultaneously reducing miR-622 expression, resulting in a decrease in cell proliferation and an increase in apoptosis induction [44]. Targeting E2F1 and controlling cell proliferation and apoptosis [54] are two ways in which miR-622 functions as a tumor suppressor in ESCC.

DNA methylation is an important mechanism for controlling chromatin structure and gene expression [58, 59], and alterations in DNA methylation status may serve as diagnostic biomarkers for cancer. Methylation of the miR-622 promoter and EZH2-dependent H3K27 trimethylation govern miR-622 downregulation in liver cancer cells. When miR-622 expression is downregulated, CXCR4 is activated, which promotes tumor growth [31]. DNA methylation has also been shown to repress miR-622 expression in HCC [55], which inhibits cell proliferation via the CCL18/MAPK signaling pathway. Both apoptosis and proliferation rely on properly functioning cell cycle control [60]. MiR-622 targets K-Ras, and studies have shown that increasing miR-622 expression in HCC improves the G1/G0 cell cycle ratio and reduces the G2 cell cycle percentage [25]. Furthermore, miR-622 targets YAP1 in glioma cells to suppress cell growth and cause G0/G1 cell cycle arrest [15]. In conclusion, miR-622 controls cell growth and death via many signaling mechanisms.

5.2. Metastasis

To a lesser extent, miR-622 can control cell invasion and migration. miR-622 suppresses migration and invasion via the hsa-circ-0000211/miR-622/HIF1-α axis in lung adenocarcinoma [18], whereas in HCC, miR-622 restricts invasion ability via the hsa_circ_0101432/miR-622/MAPK1 axis [17]. In gliomas, miR-622 has been found to target ATF2 [35], ZEB2 [36], and K-Ras [37], therefore inhibiting cell migration and invasion. Targeting genes involved in metastasis [22] is one way in which miR-622 influences prostate cancer. The metastasis of tumors caused by HCC [31], CCA [51], and glioblastoma [37] have all been shown to be influenced by the first three genes listed. Furthermore, miR-622 may restrict GC cell

invasion by focusing on ING1 [19]. Drosha reduces production of miR-622, which in turn upregulates LAMC2 expression, activates EGFR-ERK1/2 signaling, and promotes GC cell invasion [46].

A biological process known as epithelial-mesenchymal transition (EMT) occurs when quiescent epithelial cells acquire an invasive mesenchymal phenotype [61]. Inhibiting Snail, -catenin, and vimentin and lowering HIF-1 levels increases E-cadherin and impedes the EMT axis, preventing lung cancer cells from metastasizing [52]. Overexpression of miR-622 may be facilitated by ERK activation, which in turn suppresses FOXO3a [52]. miR-622 aims for HULC in pancreatic cancer. By downregulating miR-622, TGF- facilitates EMT signaling via EVs by decreasing E-cadherin expression and raising levels of Snail, N-cadherin, and Vimentin [23]. In breast cancer, miR-622 suppresses EMT and cell migration by directly regulating RNF8 [48]. Furthermore, the miR-622/NUAK1 axis has been identified to influence the motility characteristic of breast cancer cells [14].

Important to the metastatic route is angiogenesis, which is how tumor cells get into the bloodstream after escaping the initial location [62]. MiR-622 can suppress angiogenesis in CRC by targeting the CXCR4-VEGFA axis [16]. In addition to being controlled by circ_GLG1 [63], miR-622 works directly on K-Ras to reduce tumor invasion and migration [39], [63]. The opposite is true for miR-622, which targets DYRK2 and has been shown to encourage migration and invasion [40]. Tumor metastasis prevention has been shown to reduce cancer-related mortality [64]. As a result, miR-622 shows promise as a tumor biomarker for early detection and intervention, ultimately leading to better outcomes for cancer patients.

5.3. Resistance

Drug resistance is a major obstacle in the treatment of malignancies [65]. Targeting the Ku complex and rescuing homologous recombination (HR)-mediated double-strand break (DSB) repair [21], miR-622 develops drug resistance to Poly ADP-ribose polymerase inhibitors (PARPis) and platinum-based therapies in HGSOCs. Tumor resistance to sorafenib has been linked to the RAS-RAF-ERK axis [66], and a recently discovered mechanism involves the RAS pathway axis MAPK14-ATF2. Reduced expression of miR-622 mediates disinhibition of the MAPK14-ATF2 axis, which controls chemical resistance of HCC cells to sorafenib [25], and results in a lack of control of the RAS-RAF-ERK and PI3K/AKT signaling pathways. Overexpression of LIN28A, which promotes chemotherapy resistance in HCC, has been linked to loss of miR-622 [26] (Table 1), as has the targeting of LIN28A and its collaborator, ZCCHC11.

Adjuvant radioimmunotherapy for colorectal cancer shows promise [67]. Overexpression of miR-622 might enhance radiation resistance by suppressing RB expression, while miR-622 expression is dramatically upregulated in CRC cells exposed to ionizing radiation. High levels of miR-622 expression have been seen in individuals whose tumors do not regress with chemotherapy [43], suggesting that this biomarker may be used to predict the response of patients with rectal cancer to radiation. More research is needed to determine how well miR-622 expression can predict radiation resistance.

6. Conclusion

Based on our analysis, we know that miR-622 is overexpressed in many different types of cancer, and that it generally functions as a tumor suppressor by preventing the initiation and progression of malignancies. On the other hand, miR-622 has been shown to promote carcinogenesis in HGSOCs, whereas contradictory results have been reported in breast and CRC. This discrepancy calls for more research into the molecular processes of miR-622, since it reveals the importance of cell type and environment. Tumor proliferation, apoptosis, migration, invasion, and resistance are all influenced by miR-622 via distinct molecular pathways. To affect gene expression, miR-622 may either directly target mRNAs or regulate signaling pathway axis. Here, we addressed how miR-622 is tightly linked to JNK and NF-kB signaling, ERK signaling, and the K-Ras pathway, all of which indicate that it is a promising target for tumor prevention. In conclusion, miR-622 has been the subject of substantial research into its clinical features and molecular

processes in relation to malignancies. The results highlight the importance of miR-622 as a potential biomarker for different cancers. The relevance of miR-622 in clinical treatment, notably radiation, is of increased significance because of its involvement in cell function, metastasis, and resistance.

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