

An overview of miRNAs role in neurofibromatosis type 2

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DOI: 10.22034/HBB.2023.14

Received: February 6, 2023; Accepted: June 6, 2023

ABSTRACT

Neurofibromatosis type 2 (NF2) is an autosomal dominant genetic condition that causes tumorigenicity of bilateral vestibular schwannomas. microRNAs (miRNA) are 22-25 nucleotides single-stranded class of non-coding RNAs that play an essential role in mRNA regulation, mostly negatively, in many human diseases, like cancer. They are able to augment tumorigenicity (as oncomirs) or suppress the process (as tsmiRNAs). Recent studies have elucidated their multifaceted role in transcriptomics of signaling pathways that lead to establishment, development, and invasiveness of tumors. Dysregulated expression level of miRNAs has been reported in various malignancies, as well. In the present review, we aimed to summarize the role of miRNAs in NF2 tumor homing and progression and address their potential in the patients diagnosis, management, and treatment.

Keywords: Long noncoding RNA, mircoRNAs, neurofibromatosis type 2, tumorigenesis

INTRODUCTION

Non-coding RNAs (ncRNAs) refer to a diverse group of RNA transcripts that are not translated into proteins while being able to regulate the stability, transcription, or

translation of genes encoding proteins in mammals [1]. Among the detected ncRNAs having different profiles and lengths, microRNAs have attracted the most attention. They have been shown to be involved in a wide range of biological processes even in telomere shortening [2].

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They are short in length, about 18 to 23 nucleotides, participate in epigenetic modifications, and regulate diverse processes by degrading target mRNAs or inhibiting translation [3]. Blood circulating miRNAs are easy to detect and highly stable. As a result, they are promising prognostic and diagnostic biomarkers. Various cancers are reportedly associated with miRNA expression changes [4]. To date, more than 38500 human miRNAs are listed in the miRBase database (<http://www.mirbase.org>). Such molecules play a role as tumor suppressors (tsmRNA), resulting in the down-regulation of the corresponding mRNA, or as oncomirs resulting in the up-regulation of mRNA. In the last two decades, miRNAs have shown their active presence in various pathologies related to human diseases, such as cancer [5]. Studying dysregulated miRNAs in signaling pathways is a recent clinical approach against most human cancers [6]. MiRNAs can also be considered as therapeutic targets when it comes to manipulating dysregulated pathways. Different roles in different pathways were reported, including cell apoptosis, proliferation and differentiation, and tumor invasion and progression [7]. Neurofibromatoses consist of three condition [8]: Neurofibromatosis type 1

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which is characterized by benign and malignant tumors around nerves [9,10], Neurofibromatosis type 2 and schwannomatosis. Neurofibromatosis type 2 (NF2) presents as a progressive disorder with an inherited predisposition to tumors, such as bilateral vestibular schwannoma, meningioma, glioma and ependymoma. NF2 can be inherited through an autosomal dominant pattern. A sporadic form of NF2 with de novo mutation has also been reported [11,12]. The prevalence of NF2 is estimated to be 1:25,000 in North West England, 1:32258 in the United States, 1:87410 in Finland, and 1:56161 in the United Kingdom. [13] The most common manifestation of NF2 is reported to be hearing loss due to Vestibular Schwannoma (VS), which can be preceded by or associated with tinnitus. Other spinal, cranial and peripheral nerves can experience schwannomas, as well. [14] NF2 develops due to the inactivation of NF2 tumor suppressor gene on chromosome 22 (q1213), which is responsible for encoding a p rotein called Merlin (aka Schwannomin), resulting in the development of peripheral or central nervous system tumors. [15] The number of reported mutations in the NF2 gene is 466, according to Human Gene Mutation Database (HGMD) professional 2021.4

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database (Figure 1). Non-coding RNAs, including lncRNAs and miRNA, have been previously shown to have role in neurofibromatosis type 1. [16] The present review aimed to describe the role of miRNAs in the NF2 and elucidate their potential applications in clinical interventions and diagnosis.

NF2 clinical manifestations

Vestibular schwannoma

With 90 to 95 percent risk, individuals with NF2 have been seen to form bilateral vestibular nerve schwannomas. Sporadic vestibular schwannomas are also found to be more compatible with surgical interventions [17]. Studies also revealed that NF2-associated vestibular schwannomas are phenotypically multilobulated and contain polyclonal tumor cell populations [18]. These findings may explain the poor outcome of treatments compared to sporadic forms. As comparatively seen in Figure 2, NF2 patients may present other kinds of schwannomas, including subcutaneous schwannomas, peripheral nerve schwannomas, as well as other cranial nerve's tumors. All of which rarely enroll in malignancy transition processes, similar to peripheral neurofibromas in NF1 [19].

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Meningiomas

Meningioma is a common primary dural-located brain tumor. In addition to schwannomas, approximately 50 to 75 percent of patients with NF2 develop multiple meningiomas in both intracranial and spinal forms. Studies have shown that loss of chromosome 22 or different kinds of NF2 gene mutations are widely associated with meningioma development in the general population. However, the exact role of the NF2 gene and Merlin protein in meningioma molecular pathogenesis has yet to be demonstrated [11].

Ependymoma

Ependymoma refers to the neoplastic cell proliferation with molecular, histological, and ultrastructural similarities to ependymal cells in the ventricles and spinal canal, which occurs in almost 33 % to 53 % of NF2 patients and involves the posterior fossa and cervicomedullary area of the spine. Treatment is often conservative for spinal ependymoma associated with NF2 due to the absent signs in most cases and the risk of resection-associated complications. However, surgery seems useful in some patients [20].

Glioma

The detection of glioma can be a useful criterion in diagnosing NF2. About 80 % of the lesions in clinical pathology examination identified as NF2-related gliomas, are spinal intramedullary or cauda equina ependymoma. NF2 patients uncommonly present with diffuse astrocytoma and pilocytic astrocytoma for unknown reasons. Diffuse astrocytomas are often associated with NF2 changes, although usually as sporadic changes and NF2 does not appear to be significantly predisposed to produce these lesions [21].

Biogenesis of miRNAs

The biogenesis of human miRNA begins with the transcription of pri-miRNA from a single miRNA gene or a polycistronic miRNA from a group of genes having a joint promoter. The management of this process for most miRNAs is the responsibility of RNA polymerase II/III [22]. Most genes encoding miRNAs are located in intergenic regions, while some are located in intragenic regions. RNA-Induced Silencing Complex (RISC) is a multiprotein complex capable of silencing almost any kind of gene, which is programmed by small RNAs such as siRNAs and miRNAs. A target gene is

miRNAs role in neurofibromatosis type 2 silenced through formation of heterochromatin [23], inhibition of translation, and degradation of mRNA. The RISCs consist of two main domains, including a small guide RNA (to find the silencing site in the genome) and a member of the protein family of Argonaute/PIWI [16]. Argonaute proteins are assisted by miRNAs in the control of gene expression, and PIWI proteins are assisted by other small RNAs of PIWI-interacting RNAs (piRNAs). PIWI proteins have shown a vital function in germline development and gametogenesis. Mammalian cells express piRNAs mainly containing 24-32 nucleotides. A two-step maturation occurs for the pri-miRNA before it associates with the RISC complex and targets mRNAs in the cytoplasm [24]. Figure 3 demonstrates the process, graphically.

Pri- miRNA to pre- miRNA maturation

Most miRNAs are transcribed by pol RNA II, while a small group surrounded by repetitive sequences such as Alu are transcribed by pol RNA III. The transcription product by either of these two is called primary miRNA (pri-miRNA), which consists of a 5' cap and a polyadenylated tail. miRNAs are first processed in the nucleus [25]. At this stage, pri-miRNA is cut by a type of RNase called Drosha and its protein cofactor DGCR8

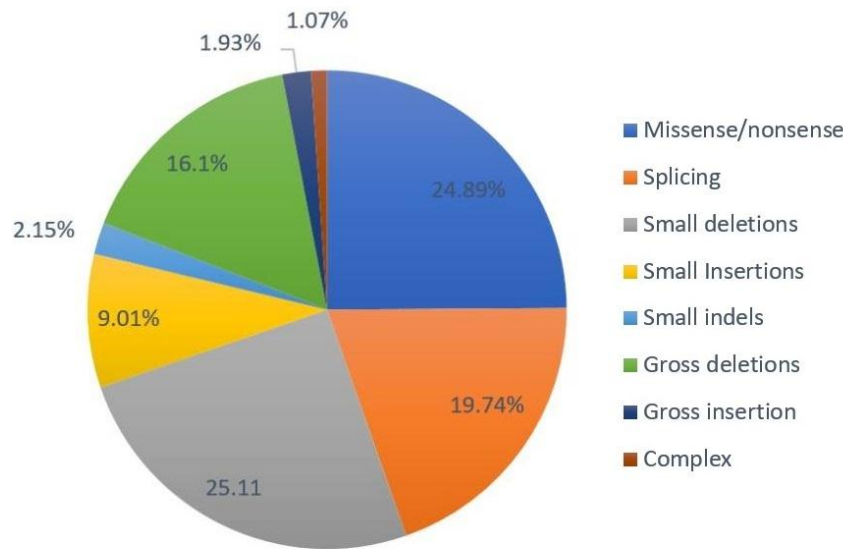
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(DiGeorge Syndrome Critical Region 8) in the hairpin region. It releases a stem-loop structure of about 70 nucleotides called precursor microRNA (pre-miRNA). DGCR8 with a single-stranded part RNA interacts and directs the Drosha to the target site, then the pre-miRNA is sent to the cytoplasm for further processing by exportin-5 [26].

Pre- miRNA to mature miRNA maturation

After pre-miRNA is released in the cytoplasm, the second processing step is performed by a cytoplasmic endonuclease

miRNAs role in neurofibromatosis type 2 called Dicer. Dicer action leads to the creation of a double-stranded RNA with a length of about 18 to 25 nucleotides. One of the strands of this duplex is degraded after binding to Argonature proteins (AGO), and the other strand is loaded on the RNA Induced Silencing Complex (RISC). The thermodynamic stability of the two ends of this duplex determines which strand is degraded. Evidence has shown that each one with a more unstable 5'-end does not break down [26].



NF2 Gene Mutations

Figure 1. Types of Gene Mutations in NF2 gene. According to the HGMD database, total number of 466 mutations have been discovered in NF2 gene. Mutations include 116 Missense/nonsense mutations, 92 splicing mutations, 117 small deletions, 42 small insertions, 10 small indels, 75 gross deletions, 9 gross insertions, 5 complex mutations.

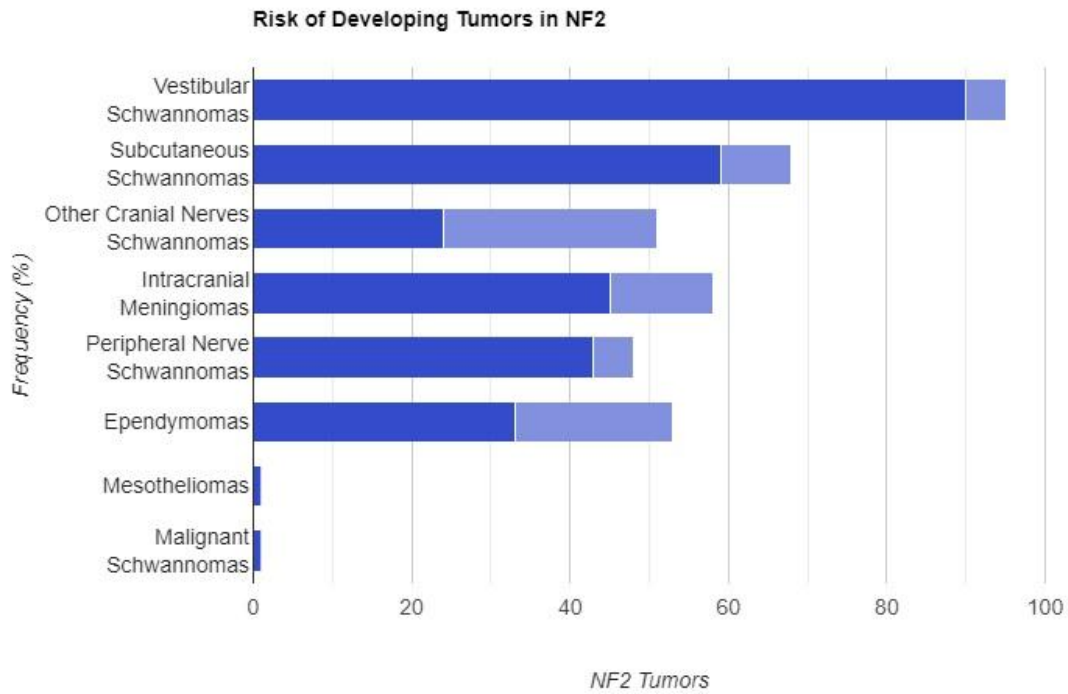


Figure 2. Loss of function mutations in NF2 gene leads to proliferation alterations, mostly due to Merlin’s role in Ras pathway. As a consequence, different kind of tumors have seen in NF2 Including Vestibular Schwannomas (90-95 %), Subcutaneous Schwannomas (59-68 %), other cranial nerves’ schwannomas (24-51 %), intracranial meningiomas (45-58 %), peripheral nerve schwannomas (43-48 %), ependymomas (33-53 %), mesotheliomas (rare), malignant schwannomas (rare).

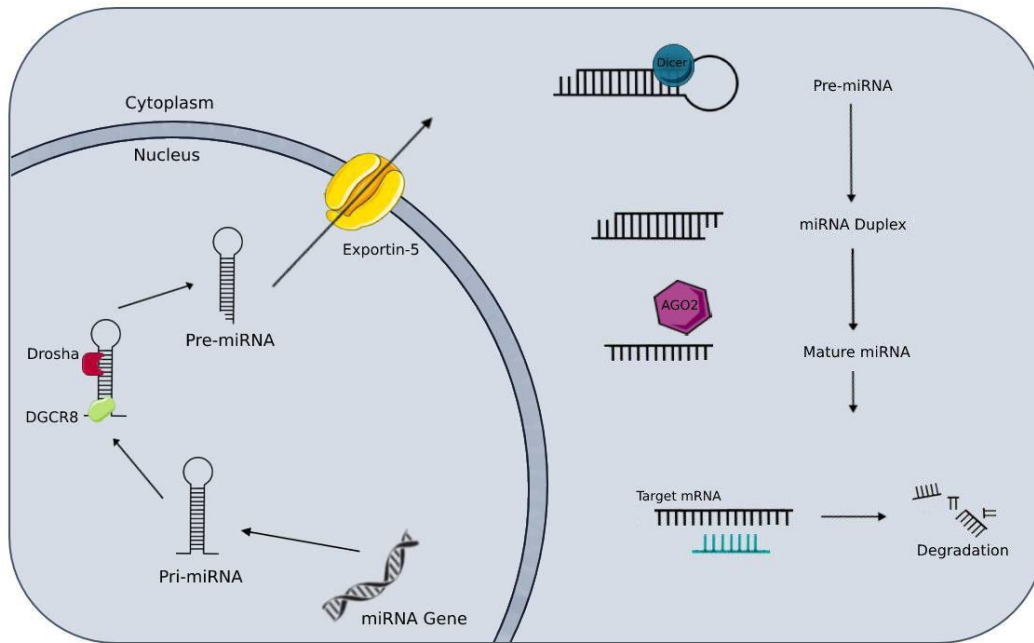


Figure 3. Graphical illustration of the two-step process of miRNA biogenesis. The first occurs within the nucleus, during which miRNA precursor (pre-miRNA) is produced from primary miRNA (pri-miRNA) transcript in presence of Drosha and DGCR8 proteins' cleavage activity. At the second step, outside of the nucleus, a protein called Dicer carries out the processing of the pre mature miRNA into the mature functional miRNA. Then the mRNA silencing occurs, consequently.

MiRNAs involved in NF2

Anti-MiR-21 agents may reduce VS cell proliferation

By achieving cancerous properties and affecting vestibular nerves, Schwann cells happen to turn into Vestibular Schwannomas (VS), which are hallmarks of NF2. Examination of miRNA expression level in VSs has indicated a possible role of miR-21. VSs found to have a higher expression level (>6 fold) of miR-21 relative to unaffected vestibular

nerve tissue. From a functional perspective, treating VSs with Anti-miR-21 leads to inhibited cell proliferation. A correlation between miR-21 upregulation and downregulation of its molecular target, PTEN, has also been reported. PTEN is a tumor suppressor with a well-known role in developing different cancers, including lung and breast. MiR-21 is one of the first discovered oncogenic miRNAs, able to silence a number of tumor suppressor genes related to proliferative and invasive features of cells.

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Therefore, it has been largely investigated for its role in tumorigenesis, including diagnostic and prognostic functions in malignant tumors. It may also be beneficial to monitor cancer therapies as viable biomarker candidates [27].

Elevated miR-200a inhibits cell growth in meningiomas

Loss of NF2 gene due to a 22q deletion event has been indicated as a common factor in meningiomas tumorigenesis. They consist of up to 20 percent of CNS tumors. Meningioma can occur with or without NF2 deletion. Evaluation of miR-200a expression profile in both types of meningiomas revealed a significant downregulation (>2 fold). The molecule inhibits Wnt/ β -catenin signaling by targeting CTNNB1 mRNA. Dysregulation of the pathway's components is found to be common in cancers. Elevating miR-200a expression, both in vivo and in vitro, results in reduced cell proliferation of meningioma tumors [28].

ACK1 is a newly identified target for MiR-7 in NF2

A 2011 study by Saydam et al. evaluated the function of miRNAs using high-throughput miRNA profiling of human vestibular schwannoma in tumor growth

miRNAs role in neurofibromatosis type 2 based on an array of 407 specified miRNAs. Tumor specimens showed a significant deregulation in 12 miRNAs when compared to control nerve tissue, indicating a typical schwannoma symptom. The miR-7 was one of the most downregulated (14-fold) within such tumors and some specified oncogene targets, such as P21-Activated Kinase 1 (PAK1) mRNA and Epidermal Growth Factor Receptor (EGFR) mRNA. The growth of schwannoma cells was inhibited in vivo due to overexpressed miR-7 in both culture and xenograft tumor models, which is associated with blocking such signaling pathways. It should be noted that these researchers introduced a new direct target of miR-7, mRNA for cdc42 kinase 1 (ACK1), which had an inverse relationship with the miR-7 and ACK1 expression levels in specimens of human schwannoma. The miR-7 can be act as a curative molecule to manage schwannoma, and that the clinical evaluation should be done for the agents capable of blocking the signaling pathways of PAK1, EGFR, and ACK1 [29]. Other deregulated miRNAs in this study are listed in Table 1. Accordingly, these miRNA sets are able to be up-regulated in a fixed pattern, presenting a

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miRNA symptom specific to schwannoma tumors.

MiR-92a downregulates NF2 gene

Inactivation of Merlin, a tumor suppressor, can result in benign nervous system tumors of NF2. This tumor suppressor can be inactivated due to detrimental mutations in the NF2 gene and aberrant Merlin proteasomal degradation. MiRNAs, can regulate NF2 by interacting with miRNA Response Elements (MREs) evolutionarily conserved in the 3'-Untranslated Region (3'UTR). According to the dual luciferase determinations in A549 and HCT116, the wild variant of NF2 was downregulated via miR-92a by its 3'UTR but in absence of MREs. The overexpressed MiR-92a in A549 and HCT116 could elevate proliferation and migration, caused apoptosis resistance, and could change the F-actin organization when comparing with controls. This attempt presents functional proof of unappreciated performance of miRNAs in the regulation of NF2 and the progression of tumor [30].

A novel miRNA, chr19_34670, identified studying VSs NF2

Vestibular Schwannoma (VS) is an intracranial tumor mostly occurred in the

miRNAs role in neurofibromatosis type 2 lateral skull base, derived from Schwann cells in the vestibular nerves, which has to subtypes based on neuroradiological appearance including cystic Vestibular Schwannoma (CVS) and Solid Vestibular Schwannoma (SVS). CVS, as an aggressive subtype of VS, has a rapid growth and poor outcomes. The molecular mechanism of CVS is unclear. A 2018 research was conducted to detect differentially expressed miRNAs between SVS and CVS tissues. Researchers could detect a new miRNA, called chr19_34670, which was downregulated in the CVS while comparing with the SVS. The 3'UTR of transforming growth factor α (TGF α) mRNA was targeted directly by chr19_34670, resulting in the suppression of its expression. The proliferation of VS cells was increased due to overexpressed TGF α , but decreased due to chr19_34670. Furthermore, the activity of main proteins was inhibited by chr19_34670 in the MAPK pathway through the suppression of MEK and ERK phosphorylation [31].

NF2 global miRNA profiling

A miRNA expression array analysis on 16 patients with VSs compared to control nerves revealed more than 60 deregulated miRNAs. Further qRT-PCR validation, narrow the number down to 10 miRNAs,

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as listed in Table 2. Among them miR-206 (fold change: 379.28), miR-10b (fold change: 269.19), miR-133b (fold change: 210.49), miR-1 (fold change: 126.72) were the most significant ones. These researchers discussed that most of these miRNAs have previously identified in other human malignancies [32].

NF2 negatively regulates miR-296-3p in glioblastoma tumors

One of the most aggressive primary brain tumors is Glioblastoma Multiforme (GBM), which arises from non-neuronal glial cells. The exact molecular mechanism of the NF2 tumor suppressor, also referred to as Merlin, is not yet fully understood. The miR-296-3p expression is down-regulated by NF2. STAT5A expression is repressed following miR-296-3p overexpression, causing STAT3 phosphorylation through SOCS2 downregulation [33]. It is demonstrated that NF2 negatively controls the invasiveness of GBM through YAP-dependent induction of CYR61/CCN1 and miR-296-3p.

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Serum miRNAs as potential NF2 biomarkers

A recent study by Imura et al, used Next Generation Sequencing (NGS) to comprehensively investigate serum miRNAs in NF2 patients. Advent of NGS tools have greatly enhanced the understanding of molecular mechanism of diseases [34]. Their results showed that serum miRNAs may be criteria to differentiate between familial and sporadic subtypes of NF2. In familial NF2 cases, they found downregulation of miR-193a and upregulation of miR-503. While in sporadic cases, Let-7b, Let-7c, and miR-200a were downregulated and miR-193a was upregulated [35].

As Figure 4 shows, this review summarizes the latest publications on the role of miRNAs in NF2. Increasing evidence has shown these molecules' negative and positive deregulation in tumor establishment and development. Based on our review, three miRNAs have been functionally studied and may be potential candidates for therapeutic purposes.

Table 1. Differentially expressed miRNAs in Saydam study

<i>Upregulated miRNAs</i>		
<i>miRNA</i>	Fold change	No. tumors
<i>Let7-d</i>	32	10/10
<i>mir-451</i>	21	9/10
<i>mir-23b</i>	20	9/10
<i>mir-221</i>	12	10/10
<i>mir-29</i>	12	10/10
<i>mir-16</i>	10	8/10
<i>mir-21</i>	8	10/10
<i>mir-138</i>	7	10/10
<i>mir-30a</i>	6	8/10
<i>Downregulated miRNAs</i>		
<i>miRNA</i>	Fold change	No. tumors
<i>mir-321</i>	-18	9/10
<i>mir-7</i>	-14	10/10
<i>mir-212</i>	-13	8/10
<i>mir-602</i>	-9	10/10
<i>mir-638</i>	-8	9/10
<i>mir-341</i>	-8	10/10
<i>mir-143*</i>	-7	10/10
<i>mir-373*</i>	-5	9/10
<i>mir-498</i>	-4	10/10
<i>mir-34a</i>	-3	7/10

Table 2. Differentially expressed miRNAs in Torres-Martin study

<i>miRNA</i>	<i>Fold change</i>
<i>mir-1</i>	126.72
<i>mir-10b</i>	269.19
<i>mir-133b</i>	210.49
<i>mir-183</i>	57.34
<i>mir-206</i>	379.28
<i>mir-221</i>	-9.62
<i>mir-370</i>	-3.13
<i>mir-431</i>	-6.38
<i>mir-493</i>	-7.99
<i>mir-720</i>	-3.49

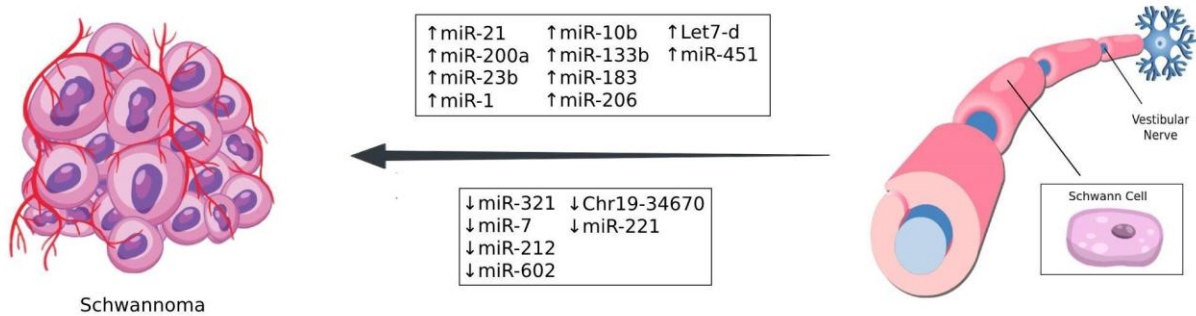


Figure 4. A summary of the role of miRNAs in tumorigenesis of VS from normal Schwann cells around vestibular nerves.

CONCLUSION

NF2 remains life-compromising without favorable treatment. About 30 years ago,

patients diagnosed with this condition had a life expectancy of only 15 years [36,37]. Augmented management strategies that lead to increased survival rate and early diagnosis have been improving the burden of the disease. However, there are still patients who die because of NF2. Age of

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onset, type of genetic mutation, and the number of meningiomas are associated with prognosis. Tumors like schwannoma and meningioma tend to progress with age, so managing the condition would be more complicated and unpredictable [38,39]. On this matter, devising new therapeutic and diagnostic methods is pivotal. Noncoding RNAs, specifically miRNAs, have been a promising strategy against human cancers [40]. Accordingly, in vitro and in vivo studies, showed that elevating the expression level of miR-7 (by blocking PAK1, EGFR, and ACK1) and miR-200a (by inhibiting CTNNB1) would have curative effect on VS and meningioma, respectively. Anti-miR-21 agents are also possible therapeutic option. Future studies should clinically investigate these candidates. NF2 symptoms may vary from patient to patient. Also, it is not clear that why the probability of having associated tumors rather than VS is varied. To date, no study has been conducted on the role of noncoding RNAs in NF2 patients with ependymoma or glioma. In this regard, miRNAs may act as useful biomarkers to differentiate and establish a classification for NF2. For example, miR-200a can be a candidate biomarker for meningioma-associated NF2, which occur in about half of the cases. Underlying mechanism of

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miRNAs biology is a field of study to grow. They are crucial mediators in various processes, through gene targeting. It is necessary to mention that most of dysregulated miRNAs in the present review are not specific to NF2, and have been shown to participate in other diseases, as well. Therefore, more studies need to be done to clarify the miRNAs weight in pathophysiological processes.

ACKNOWLEDGEMENT

We appreciate the supports of Human Genetics department of Golestan University of medical sciences.

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