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Role of microRNAs in non-functioning pituitary adenoma

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NARRATIVE REVIEW

Role of microRNAs in non-functioning pituitary adenoma

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Abstract

Non-functioning pituitary adenomas account for 30% of anterior pituitary tumours. Based on their inability to secrete hormones, these are often diagnosed incidentally or due to pressure symptoms. Understanding the pathogenesis of these adenomas can provide insight into factors leading to its progression and serving as biomarkers for early recognition. A literature search was performed in the current narrative review for articles published in PubMed for the last 10 years till January 2020 on micro-ribonucleic acid involved in the pathogenesis of non-functioning pituitary adenomas. Of the 478 articles found, 21(4.4%) were filtered. In total, 106 micro-ribonucleic acids were identified, 25(23.5%) of which appeared in more than one study. Among them, 7(28%)were up-regulated, 11(44%) down-regulated, and 7(28%) were either up- or down-regulated. Micro-ribonucleic acids allow the screening, diagnosis and treatment of diseases in a relatively easy and inexpensive manner. This can revolutionise tumour management in the years ahead, especially in resource-constrained low- and middle-income countries.

Keywords: microRNA, Non-functioning pituitary adenoma, Pathogenesis, Pituitary adenoma, Target genes, Cell signalling pathways.

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Introduction

Pituitary adenomas (PA) are a varied group of lesions of the anterior pituitary. The prevalence of clinically significant pituitary tumours is 80-100 per 100,000.[1] Majority are benign and slow-growing, but up to 10% are more aggressive. These tumours are the third most common neoplasm of the central nervous system (CNS), accounting for 15%, while the top two are meningiomas and gliomas. Based on the status of hormone secretion, these are classified as functioning (FPAs) and non-functioning pituitary adenomas (NFPAs). About 30% of all PAs are NFPAs, making it the second most frequent PA, preceded by prolactinomas that account for 50%.[2]

Unlike functioning PAs, NFPAs remain undiagnosed due to the absence of clinically evident symptoms of hormone disturbance. They are either detected incidentally or when they grow to become macroadenomas, causing pressure effects, resulting in headaches and visual field defects that are at times irreversible. Therefore, the diagnosis of NFPAs at an early stage is very crucial. Since these adenomas do not secrete hormones excessively, other factors, which are abnormally circulated in blood, can mark the presence of these tumours at an early stage. Such factors include micro-ribonucleic acids (miRNAs) which have been studied in several tumours, including NFPA.

The miRNAs are small 21-23 nucleotide, non-coding, single-stranded RNAs that regulate post-transcriptional protein-coding genes expression by targeting messenger RNAs (mRNAs) forming base pairs at the 3',5' untranslated regions or within the coding sequence.[3] Frequent involvement of miRNAs in genesis, invasion and therapeutic outcomes of several tumours have been increasingly studied and proven in literature.[2,4] The aberrant miRNAs expression has also been identified in pituitary tumorigenesis as well as in other tumours arising in the brain, such as glioma, and tumours originating from extra-cranial organs, such as prostate, ovary, breast, stomach, and liver. Pathogenesis of NFPAs has not been well established and is hypothesised to include genetic or epigenetic mutations, hormonal stimulation, growth factor overproduction, pituitary stem cell derangements and aberrant miRNA expression.[4]

The current narrative review was planned to summarise the miRNAs and its target genes involved in the pathogenesis of NFPAs.

Methods

A systematic search for literature was performed on PubMed database using Endnote X8 of the last 10 years until January 2020. The key words used were 'microRNA non-functioning pituitary adenoma', 'microRNA pituitary adenoma', 'microRNA pathogenesis non-functioning pituitary adenoma, microRNA pituitary, 'pathogenesis non-functioning pituitary adenoma', 'pathogenesis non-secretory pituitary adenoma'. All the articles identified were subjected to careful deletion of duplicate articles. All studies which evaluated miRNAs in NFPAs were included.

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Papers which evaluated FPAs or where the adenoma type was not mentioned explicitly were excluded. Review articles and studies on animal models were also excluded. Those studies which only evaluated the associated genes in the pathogenesis of NFPAs were also left out.

Results

Of the 478 articles found, 21(4.4%) were included for detailed review (Table 1). In total, 106 mi-RNAs were identified (Table 2) Of them, 25(23.5%) appeared in more than one study; 7(28%) up-regulated, 11(44%) down-regulated, and 7(28%) either up- or down-regulated (Figure).

The 7 up-regulated miRNAs were mir-181 (4 studies), mir-106 (3 studies), mir-155, mir-582, mir-182 and mir-301 and mir-137 (2 studies). The 11 down-regulated miRNAs were mir-370 (4 studies), mir-503 and mir-134 (3 studies each), mir-450, mir-214, mir-410, mir-199, mir-508, mir-493, mir-23 and mir-34 (2 studies each). Mir-26 (downregulated in 2 and upregulated in 1 study), mir-128, mir-516, mir-140, mir-124, mir-146 and mir-149 (downregulated/upregulated in 1 study each) constituted the 7 mixed types.

The reported miRNAs from some of these studies were linked back to the target genes involved in cell cycle regulation or cell signalling pathways and vice versa in the studies where aberrant expression of genes were identified.

Cell Cycle Regulators: Wee1Kinase, a cell cycle regulator, was found to be associated with up-regulation of mir-128, mir-516 and mir155.[5] Another cell cycle regulator Cyclin

Table 1: Studies included in the systematic review.

Study Title (Author, Year)	Population (Country)	Adenoma tissues	Non-tumour tissues	Methodology Techniques used	Upregulated miRNAs	Downregulated miRNAs
Butz, H., et al. (2010)[5]	Hungary	56	15	qRT-PCR	mir-128a, miR-155, miR-516a-3p	-
Butz, H., et al. (2011)[16]	Hungary	20	10	TLDA miR array	miR-135a, miR-140-5p, miR-582-3p, miR-582-5p, miR- 938 and miR-592	miR-450b-5p, miR-424, miR-503, miR-542-3p, miR-629 and miR-214
Cheunsuchon, P., et al. (2011)[17]	USA	44	-	qRT-PCR.	-	miR-134, miR-323, miR-370, miR-410, and miR-432
Palmieri, D., et al. (2012)[18]	France	41	-	qRT-PCR	-	miR-15, miR-16, miR-26a, miR-196a2 and Let-7a
Trivellin, G., et al. (2012)[19]	UK	19 (global miRNA expression) 49 (miR-107 expression)	5	TLDA assays and RT-qPCR	miR-107	-
Liang, S., et al. (2013)[20]	China	22	2	RT-PCR with SYBR GREEN I	NFPA: hsa-miR-124a, hsa-miR-146a, MIR240, hsa-miR-523, hsa-miR-10b, MIR207, hsa-miR-182, MIR220, hsa-miR-520b, MIR112, hsa-miR-144, hsa-miR-373, hsa-miR-422b, hsa-miR-202, hsa-miR-520e, hsa-miR-32, hsa-miR-422a, hsa-miR-181c, MIR206, hsa-miR-181b, hsa-miR-520c, MIR166, hsa-miR-188, hsa-miR-155, hsa-miR-520f)	NFPA: hsa-miR-31, hsa-miR-514, hsa-miR-503, hsa-miR-506, hsa-miR-513, hsa-miR-218, hsa-miR-509, hsa-miR-199b, hsa-miR-508, hsa-miR-489, hsa-miR-212, hsa-miR-493, hsa-miR-450, hsa-miR-363, hsa-miR-424)
Leone, V., et al. (2014)[21]	Italy	41	5	qRT-PCR	-	miR-23b and miR-130b

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Table-1: *continued from previous page.*

Study Title (Author, Year)	Population (Country)	Adenoma tissues	Non-tumour tissues	Methodology Techniques used	Upregulated miRNAs	Downregulated miRNAs
Wei Z, et al. (2015)[22]	China	2	-	High-throughput human microRNA microarrays, TaqMan microRNA arrays and qRT-PCR	miR-20a, miR-106b and miR-17-5p	-
Yu C, et al. (2016)[23]	China	70	12	qRT-PCR	MiR-26a	-
Zhou K, et al. (2016)[24]	China	55	8	MTT assays, Transwell Assay and qRT-PCR	miR-106b	-
Butz, H., et al. (2017)[25]	Hungary	94	14	TLDA assays and RT-qPCR	-	miR449a, miR449b, miR424 and miR503
Wu S, et al. (2017)[26]	China	20	-	qRT-PCR using TaqMan microRNAs Assay	hsa-miR-181b-5p, hsa-miR-181d, hsa-miR-191-3p, and hsa-miR-598	hsa-miR-3676-5p and hsa-miR-383
Zhen, W., et al. (2017)[27]	China	20	8	qRT-PCR	-	miR-524-5p
Zheng Z, et al. (2017)[28]	China	50	10	qRT-PCR	miR-106b	-
Song W, et al. (2018)[29]	China	168	5	qRT-PCR	miRNA-137, miRNA-374a-5p and miRNA-374b-5p	-
Cai F, et al. (2019)[30]	China	75	-	RT-PCR	-	miR-134 and miR-370
Darvasi O, et al. (2017)[31]	Hungary	8	4	SOLiD next-generation-sequencing, Microarray and qRT-PCR	mir-137, mir-149, mir-182, mir-183, mir-301a, mir-429, mir-582, mir-628, mir-660, mir-885, mir-935, mir-95, mir-96	mir-134, mir-193a, mir-214, mir-34a, mir-370, mir-379, mir-382, mir-433, mir-487b, mir-497, mir-510,mir-770
He, Z., et al. (2019)[32]	Southwestern China provinces	73	6	NGS, RNA deep sequencing and qRT-qPCR	NFPA: miR-181b-5p GHPAs: miR-184	PRLPAs: miR-34c-3p, miR-34b-5p, miR-378 and miR-338-5p NFPA: miR-493-5p, miR-124-3p GHPAs: miR-124-3p
Joshi, H., et al. (2019)[33]	India	7	3	Pathway Enrichment Analysis, Gene Ontology Enrichment Analysis and Module Analysis	-	-
Vicchio, T. M., et al. (2020)[34]	Italy	23	5	qRT-PCR	-	miR-516-3p, miR-151a-3p, miR-455-3p, miR-29b-3p, miR-508-5p, miR-199a-5p, miR-23b-5p, miR-34b-5p, miR-26b-5p, miR-128-3p, miR-30a-5p, miR-140-5p, miR-149-3p, miR-146a-5p, 130a-3p, miR-648, miR-370-3p
Zhu, D., et al. (2020)[35]	China	30	12	qRT-PCR	-	MEG3 and MIR-376B-3P

Table-2: Summary of 106 microRNAs associated with NFPA.

S#	microRNA	Regulation	Target (Gene/ Protein)
1	mir-128a[5]	Up	Wee1 kinase
	mir-128-3p[34]	Down	CYCLIN K, TGFBR1, CASP8, RPS6KA5, JAG1, RAB8B
2	mir-155[5,20]	Up	Wee1 kinase
3	mir-516a-3p[5]	Up	Wee1 kinase
	mir-516-3p[34]	Down	AHRR, BCL2, CBLB, PCDH7
4	mir-135a[5]	Up	SMAD3
5	miR-140-5p[5,34]	Up	SMAD3
		Down	SMAD3, TGFBR1, HDAC7, CASP3, FGF9
6	miR-582-3p[5]	Up	SMAD3
	miR-582-5p		
	mir-582[31]		-
7	mir- 938[16]	Up	SMAD3
8	mir-592	Up	-
9	mir-450b-5p[16]	Down	-
	mir-450[20]		
10	mir-424[16,20]	Down	-
11	mir-503[16,20,25]	Down	-
			-
			CDC25A
12	mir-542-3p[16]	Down	-
13	mir-629		
14	mir-214[16,31]	Down	-
15	mir-134[17,30,31]	Down	DLK1-MEG3 locus
			VEGFA and ABCC1
			-
16	mir-323[17]	Down	DLK1-MEG3 locus
17	mir-370[17]	Down	DLK1-MEG3 locus
			-
	mir-370–3p[31,34]	Down	HMGA2 and MAP3K8
			MAP3K8, HDAC4, PIK3CA
18	mir-410[17,25]	Down	DLK1-MEG3 locus
			CDK1
19	mir-432[17]	Down	DLK1-MEG3 locus
20	mir-377		
21	mir-299-5p		
22	mir-329		
23	mir-15[18]	Down	HMGA1/2 genes
24	mir-16		
25	mir-26a[18,23]	Down	HMGA1/2 genes
		Up	PLAG1
	miR-26b-5p[34]	Down	CDK8, TTK, ARNT2, PTEN, PAK2, PRKCD, FGF9, PTEN, MTDH, JAG1
26	mir-196a2[38]	Down	HMGA1/2 genes
27	Let-7a		
28	mir-107[39]	Up	AIP gene
29	mir-124a[20]	Up	-
	mir-124-3p[32]	Down	-
30	mir-146a[20]	Up	-
	mir-146a-5p[34]	Down	CYCLIN J, NRAS, TRAF6, CEMIP
31	mir-240[20]	Up	-
32	mir-523		
33	mir-10b		
34	mir-207		

Continued on next column.

Table-2: *continued from previous column.*

S#	microRNA	Regulation	Target (Gene/ Protein)
35	mir-182[20,31]	Up	-
		Up	-
36	mir-220[20]	Up	-
37	mir-520 b,c,e,f		
38	mir-112		
39	mir-144		
40	mir-373		
41	mir-422a, b		
42	mir-202		
43	mir-32		
44	mir-181c		
	mir-181b		
	mir-181b-5p [26,32]	Up	TCF3, CYP26A1, MYC, SREBF1, and MAX
			-
	mir-181d[26]	Up	TCF3, CYP26A1, MYC, SREBF1, and MAX
	mir-181d-5p[33]	-	CCND2, SCD, VAV3, CDK6, PEG10
45	mir-206[20]	Up	-
46	mir-166		
47	mir-188		
48	mir-379[31]	Down	-
49	mir-382		
50	mir-433		
51	mir-487b		
52	mir-497		
53	mir-510		
54	mir-770		
55	mir-149[31]	Up	-
	mir-149-3p[34]	Down	SMAD3, MKNK2, FAIM2, TNS1, RAB11B
56	mir-183[31]	Up	-
57	mir-301a	Up	-
	mir-301a-3p[33]	-	-
58	mir-429[31]	Up	-
59	mir-628		
60	mir-660		
61	mir-885		
62	mir-935		
63	mir-95		
64	mir-1976[33]	-	HS3ST1, GPC4, KCNJ6, THBS2, CBS
65	mir-4491		
66	mir-1202		
67	mir-501-3p		
68	mir-548a-5p		
	mir-548p		CCND2, SCD, VAV3, CDK6, PEG10
69	mir-1825		
70	mir-1179		
71	mir-151a-3p[34]	Down	RPS6KA5, PKN2, AKT3
72	mir-455-3p		TTK, AHR ,HDAC2, BAG4
73	mir-29b-3p		TGFB2, HDAC4, SIRT1, TNFRSF1A
74	mir-128-3p		CYCLIN K, TGFBR1, CASP8, RPS6KA5, JAG1, RAB8B
75	mir-30a-5p		CYCLIN E2, CYCLIN K, CDK12, MAPK1,
TGFA, CASP3, CBLB, MTDH			
76	mir-130a-3p		MAPK1, TGFBR1, MDM4, PTEN, PTEN, RAP2C, RAB9B
77	mir-648		RAD21, THBS1, TRIAP1, RAB8B, RAB1A

Continued on next column.

Table-2: *continued from previous column.*

S#	microRNA	Regulation	Target (Gene/ Protein)
78	mir-376b-3p[35]	Down	MEG3
79	mir-31[20]	Down	-
80	mir-514,		
81	mir-506		
82	mir-513		
83	mir-218		
84	mir-509		
85	mir-199b[20]	Down	-
	mir-199a-5p[34]		SMAD3, TGFB2, TGFA, TGFBR1, SMAD3, SIRT1, IKBKB, JAG1
86	mir-508[20]	Down	
	mir-508-5p[34]		CHEK1, CYCLIN J, TFDP2, CYP3A4, FASLG, FAIM1
87	mir-489[20]	Down	-
88	mir-212		
89	mir-493[20]	Down	-
	mir-493-5p[32]		
90	mir-363[20]	Down	-
91	mir-23b[21]	Down	HMGA2 gene
	mir-23b-5p[34]		ARNT, CEMIP
92	mir-130b[21]	Down	cyclin A2 gene
93	mir-20a[22]	Up	PTEN & TIMP2
94	mir-106b[22,24,28]	Up	PTEN & TIMP2
			PTEN
			PTEN
95	mir-17-5p[22]	Up	PTEN & TIMP2
96	mir-449a,b[25]	Down	CDC25A
97	mir-24[25]	Down	CDK1
98	mir-3676-5p[26]	Down	TCF3, CYP26A1, MYC, SREBF1, and MAX
99	mir-383		
100	mir-191-3p	Up	
101	mir-598		
102	mir-524-5p[27]	Down	PBF
103	mir-137[29,31]	Up	WIF1 and sFRP4
104	mir-374a-5p[29]	Up	WIF1 and sFRP4
	mir-374b-5p		
105	mir-193a[31]	Down	-
106	mir-34a[31]	Down	
	mir-34b-5p[34]	Down	CYCLIN E2, MTDH, RAB3C

NFPA: Non-functioning pituitary adenomas, LMICs: Low- and middle-income countries, PA:Pituitary adenomas, GH: Growth hormone, ACTH: Adrenocorticotrophic hormone, PRL: Prolactin, TSH: Thyroid-stimulating hormone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, MRI: Magnetic resonance imaging, mRNAs: Messenger ribonucleic acids, NSCLC: Non-small cell lung cancer, GBM: Glioblastoma multiforme, HCC: Hepatocellular carcinoma, ceRNA: Competing endogenous RNA, MREs: microRNA response elements, miRNA: MicroRNA, SMAD3 = Mothers against decapentaplegic homolog 3, TGF-B = Transforming growth factor beta, HMGA = High-mobility group A, EMT = Epithelial–mesenchymal transition, AHR = aryl hydrocarbon receptor, MAPK = mitogen-activated protein kinase, PI3K/AKT = phosphatidylinositol 3-kinase/protein kinase B, PTEN = Phosphatase and Tensin Homolog, p53 = Tumor protein 53, Jak-STAT = Janus kinases signal transducer and activator of transcription proteins , mTOR = Mammalian target of rapamycin, Raf = Rapidly Accelerated Fibrosarcoma, MEK = mitogen-activated protein kinase, ERK = extracellular-signal-regulated kinase and Rab = Ras-associated binding (Rab) proteins, GTPases = GTP-binding proteins

with three subtypes Cyclin K, Cyclin J and Cyclin E2 were all linked to the decreased expression of mir-128 (Cyclin K), mir-146 and mir-508 (Cyclin J) and mir34 (Cyclin E2)).[6]

Down-regulation of SMAD3 (Mothers against decapentaplegic homolog 3), which is an intracellular mediator of TGF-B (Transforming growth factor beta) pathway, is correlated with the altered expression of several miRNAs: down-regulation of mir-149, mir-199, mir-140 and up-regulation of mir-140 and mir-582. Mir-26,[7] mir-370[8] and Mir-23[9] were found to be down-regulated, resulting in over-expression of HMGA1/2 (High-mobility group A) proteins, causing tumour invasiveness in NFPAs.

Cell Signalling Pathways: Dysregulated miRNAs also target several cell-signalling pathways. A total of 11 pathways were linked to these deregulated miRNAs. Vicchio et al.[6] stated numerous targeted genes in several pathways and linked them to down/upregulated miRNAs: the apoptosis pathway, linked to 8 down-regulated miRNAs: mir-128, mir-516, mir-140, mir-26, mir-149, mir-370, mir-199, mir-508; EMT (Epithelial–mesenchymal transition) pathway associated downregulated miRNAs: mir-26, mir-146, mir-23 and mir-34; AHR (Aryl hydrocarbon receptor) pathway associated down-regulated miRNAs: mir-515, mir-26, mir-23; Notch signalling pathway associated with mir-128, mir-26 and mir-199; MAPK (Mitogen-activated protein kinase) pathway related to downregulated mir-146, mir-149 and mir-370; TGF beta (Transforming growth factor beta) pathway downregulated mir-128, mir-140, mir-149 and mir-199. Aberration of PI3K/AKT (phosphatidylinositol 3-kinase/protein kinase B) pathway via PTEN (Phosphatase and Tensin Homolog) was also reported in several studies via downregulation of mir-140, mir-26 and upregulation of mir-106.[10]

Discussion

MiRNAs are small non-coding nucleotide RNA that binds to mRNA to control post-transcriptional gene expression regulating cell growth. The involvement of several differentially expressed miRNAs in the pathogenesis of NFPA has been extensively reported in literature.[6] These miRNAs have also been found to be dysregulated in tumours of other regions acting as tumour suppressors or oncogenes by targeting tumour-suppressor genes or tumour promoter genes such as mir-181, which is downregulated in glioma[11] and non-small cell lung cancer (NSCLC)[12] and mir-134, which is downregulated in renal cell carcinoma, colorectal cancer, hepatocellular carcinoma (HCC), glioma, endometrial cancer, and osteosarcoma. To date, studies have shown multiple miRNAs acting on various signalling pathways, such as MAPK (mitogen-activated protein kinase), p53 (Tumour protein 53), TGFβ, Jak-STAT(Janus kinases signal transducer and activator of transcription proteins), PI3K/Akt/mTOR (Mammalian target of rapamycin) and Raf(Rapidly Accelerated Fibrosarcoma)/MEK(mitogen-activated protein kinase)/ERK (extracellular-

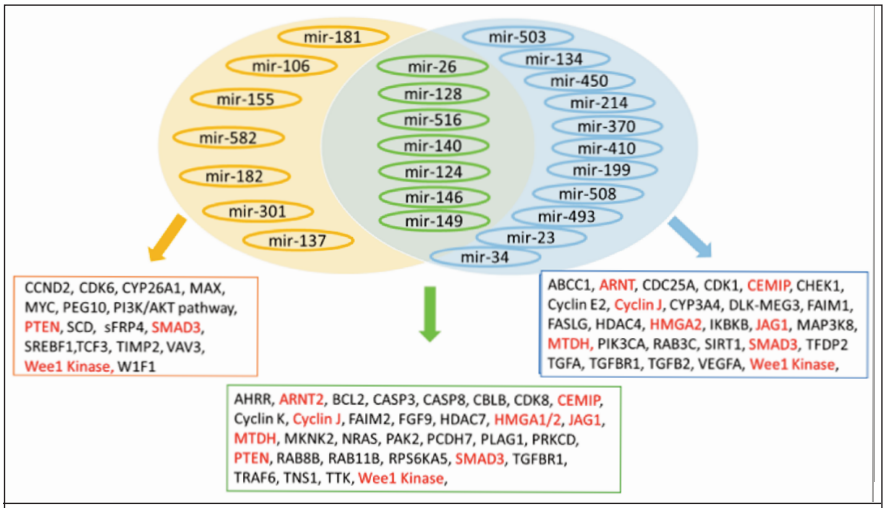

Figure: A total of 7 up-regulated (orange), 11 down-regulated (blue) and 7 either up/down-regulated (green) microRNAs and their associated target genes. Genes that are targeted by all types (up/down) of microRNAs are coloured red (More details are given in Table 2).

signal-regulated kinase). These observed pathways and miRNAs have led to the thesis that a very complex interaction network might be the crux in the pathogenesis of NFPA. This network provides insight into numerous novel target sites that can be used for the diagnosis and treatment of tumours.

MiRNAs also play a role in hormone secretion, therefore NFPAs can be differentiated from other PAs based on preferential miRNAs expression profile even before symptoms become apparent. The miR-149-3p is expressed 13 times more in growth hormone-secreting adenomas compared to NFPA, possibly due to action on Rab GTPases (Ras-associated binding (Rab) proteins GTP-binding proteins).[13] The current review demonstrates a comprehensive list of miRNAs that are dysregulated in NFPA to varying degrees. Some of these miRNAs or intermediates in their pathways can potentially be detected via probes for non-invasive diagnosis of NFPA. Taking a step further, a panel of miRNA can also be created which will allow several target regions to be detected altogether leading to an increase in specificity and sensitivity of diagnostic tests in the future.

Because studies have associated differential miRNAs expression with clinical profiles of patients, the miRNAs analysed in this site can be used to study the progression and aggressiveness of tumours in patients. In NFPA, a relationship was found between deregulated miR-508-5p and aggressive clinical behaviour of the patient.[6]

These are some of the uses that rely on the detection of miRNAs mainly with the aim of diagnosis and prognosis. However, the real target of this rapidly progressing field is the development of miRNA-based therapies that can provide novel anti-tumour treatments even for patients who are resistant to currently available options. Moreover, a new use of miRNAs has been to monitor the response of current treatments which has led to the emergence of personalised medicine, the promise of modifying treatments for every individual to get the best outcomes possible. Downregulated miR-370 is found to increase resistance to temozolomide in patients of glioblastoma multiforme (GBM) and when the levels of miR-370 increased, the sensitivity to temozolomide therapy also increased significantly.[14]

Expert Opinion: The multiplicity of miRNAs can provide a rich source to help unravel the mysteries around the diagnosis of NFPA. Although miRNAs do not code for specific amino acids, they regulate gene expression that is crucial for many physiological processes. Their aberrant expression in the tissue and presence in the blood stream can disclose important information regarding various pathological disorders. The miRNA expression profiling has proven to provide in-depth insight regarding various diseases and serve as a biomarker for many tumours. These miRNAs, like the ones discussed in this review, show that various inflammatory pathways and genes are affected in the pathogenesis of tumours. Clinicopathological associations with these miRNAs have allowed their usage as screening, prognostic and diagnostic markers that can even monitor the growth of tumours in the body and can be promising therapeutic targets for these tumours soon both of which are discussed below:

Liquid Biopsy: As miRNAs are very small in size and can escape degradation, they are relatively stable in blood and other body fluids. These circulating miRNAs can be extracted from the body fluids and quantified through liquid biopsy. This technique combines all of the circulating miRNAs in a panel providing quantitative information regarding their levels in a particular disease in comparison to healthy tissue or blood, thus serving as biomarkers for those diseases. This approach has been used widely for various cancers, such as oesophageal, gastric, colorectal, and have shown that miRNAs are highly efficient diagnostic biomarkers with specificity and sensitivity ranging from 70% to 100%. Detecting all circulating miRNA using liquid biopsy has an added advantage of diagnosing diseases at an early stage that might not be otherwise identified using traditional methods. As NFPAs are usually diagnosed at a

later stage, this procedure can be helpful in its early diagnosis. Additionally, this technique can be invaluable resource to analyse the response to any targeted therapy and for recurrence, paving the way for personalised medicine for patients.

Liquid biopsy is a simple and inexpensive technique that can be used to detect NFPAs at an early stage. In the context of low- and middle-income countries (LMICs), like Pakistan, where about a quarter of the population lives below the poverty line along with inadequately funded healthcare system, liquid biopsy can be a cost-effective resource for early tumour detection.

The miRNA Sponge: The miRNAs bind to mRNA on a specific site called miRNA response elements (MREs). MREs can be blocked by miRNA sponges or competing endogenous RNA (ceRNA), thereby blocking the regulatory effect of miRNA. There is evidence of these miRNA sponges showing anticancer effect both in vitro and in vivo, in HCC cell lines and lung cancer, respectively.[15] Artificially blocking the physiological process and implementing it as a treatment modality can prove to be a promising novel tool in fighting against aggressive tumours. Although this is an evolving approach to treating cancers, it can be safely assumed that many patients will be successfully treated using gene-based therapies in the next decade or so, which will phase out high-risk surgical procedures gradually.

Conclusion

The narrative review provides a summary of dysregulated miRNAs in the context of NFPAs, and points to downstream effects of miRNA expression and the pathways involved which has uncovered a number of potential miRNAs that studies have shown to contribute to the pathogenesis, tumourigenesis, recurrence and treatment. In the light of the review, further studies to assess the role of tumour suppressor miRNAs in targeted treatment and oncogenic miRNAs as early biomarkers of NFPAs can be performed.

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