miRNA in Pituitary Adenoma

Subjects: Clinical Neurology
Contributor: Wentao Wu , Lei Cao , Yanfei Jia , Youchao Xiao , Xu Zhang , Songbai Gui

Pituitary adenoma (PA) is a common intracranial tumor without specific biomarkers for diagnosis and treatment. Non-coding RNAs (ncRNAs), including microRNAs (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA), regulate a variety of cellular processes, such as cell proliferation, differentiation, and apoptosis. The miRNA, a small, endogenous, single-stranded, non-coding RNA with a length of 19 to 25 nucleotides that inhibits post-transcriptional protein synthesis via binding to the 3′-untranslated region (UTR) of target messenger RNAs (mRNAs), plays an important role in a variety of essential and biophysiological processes including cell proliferation, differentiation, and apoptosis. Accumulating studies have shown the dysfunction of miRNAs in human biological fluids and in cell-free environments, suggesting that these miRNAs can function as oncogenes and tumor suppressors. These important findings may contribute to provide novel diagnostic and prognostic biomarkers for PA.

biomarker pituitary adenomas miRNA

1. Circulating miRNA and Pituitary Adenoma (PA)

In 2008, circulating miRNA (c-miRNA) was detected in peripheral blood [1][2][3]. Compared to that of cellular RNA, the expression of c-miRNA is very stable in the RNase-rich environments of human biofluids due to its binding to specific proteins (e.g., the Argonaute (Ago 2) protein) [4][5]. In addition, c-miRNAs have been shown to be resistant to harmful conditions, such as high temperature, acidic or alkaline environments, and repeated freeze–thaw cycles [1][6]. Therefore, c-miRNAs are ideal candidates for novel noninvasive blood biomarkers for different types of diseases, and c-miRNAs contribute to diagnosis, prognosis, and postoperative monitoring for PA with aggressive behavior and non-functional PAs (NFPAs).

The RNA sequencing (RNA-seq) of plasma samples showed that there were several DE miRNAs in preoperative and postoperative patients with PA, including 3 DE miRNAs in a growth hormone (GH) group, 7 in an FSH/LH group, and 66 in a hormone-immunonegative (HN) group [7]. Subsequently, some DE miRNAs (i.e., miR-143-3p in FSH/LH, and miR-26b-5p, miR-126-5p, and miR-148b-3p in HN) were used for validation by real-time polymerase chain reaction (qRT-PCR) [7]. Circulating miR-143-3p was significantly upregulated in patients with preoperative FSH/LH compared to patients with postoperative FSH/LH+ [7].

Furthermore, the tumor size in patients with postoperative follicle-stimulating hormone/luteinizing hormone (FSH/LH) decreased significantly, which may result in a decrease in circulating miR-143-3p [7]. Circulating miR-143-3p exhibited a strong differentiation power, with an area under curve (AUC) value of 0.79 between

preoperative and postoperative patients with FSH/LH PAs [7]. The plasma miR-143-3p decreases in patients with FSH/LH+ adenoma, but its application in the evaluation of tumor recurrence needs further investigation [7]. These findings suggest that plasma miR-143-3p decreases may be a potential biomarker for patients with FSH/LH+ adenoma after transsphenoidal surgery. In addition, some studies have also found that miR-143 was significantly downregulated in PA tissues [8][9], and inhibited tumor proliferation by targeting the K-Ras gene [8].

Belaya et al. evaluated whether miRNAs were DE in plasma samples from patients with adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome (CS) caused by either ectopic ACTH secretion (EAS) or Cushing's disease (CD) [10]. In their study, 21 miRNAs were measured [10]; the circulating levels of miR-16-5p, miR-145-5p, and miR-7g-5p were altered; and miR-16-5p had the most distinguished power, with an AUC value of 0.879. Therefore, these results indicate that c-miRNAs are promising biomarkers for distinguishing between CD and EAS.

In addition to biomarkers for diagnosis and prognosis, c-miRNAs were also associated with the survival time for PA. Compared to that in healthy controls, the serum expression of miR-16 was decreased in patients with PA, whereas higher levels of miR-16 were accompanied by longer overall survival (OS) times and disease-free survival (DFS) times [11]. In vitro, miR-16 inhibited the proliferation and angiogenesis of PA via regulating the VEGFR2/p38/NF-κB pathway [11]. Consequently, miR-16 may be a potential target for the treatment of PA.

In conclusion, c-miRNAs have an important role for the diagnosis and prognosis of PA, but also for the treatment of PA. In the future, the research directions of c-miRNAs may lead to the translation of potential candidates with important roles in the development of the disease to their implementation as biomarkers for the diagnosis and prognosis of PA in clinical practice.

2. miRNA in PA Tissue

Some studies have shown that the abnormal expression of miRNAs in tumor tissues was significantly associated with the levels of miRNAs released into the peripheral circulation [12][13][14], suggesting that the change in miRNAs in PA tissues is implicated in the occurrence and progression of the disease.

In 2005, several DE miRNAs between normal pituitary tissues and PAs were identified [15]. Subsequent studies have shown that miRNAs may be involved in tumorigenesis, invasion, and aggressiveness as oncogenes and as tumor suppressors. Using the HiSeq 2000 sequencing system, several distinctive miRNA expression patterns were identified in three different PAs (i.e., NFPAs, GHPAs, and PRLPAs) [16]. Compared to normal pituitary tissues, significant downregulation of miR-34c-3p, miR-34B-5p, miR-378, and miR-338-5p in PRLPA; downregulation of miR-493-5p and upregulation of miR-181b-5p in NFPA; and significant upregulation of miR-184 in GHPA were observed. In addition, downregulation of miR-124-3p in both NFPA and GHPA was observed [16]. These miRNA signatures may be promising therapeutic biomarkers for different types of PA. A few studies investigated aggressiveness-associated miRNAs in aggressive pituitary tumors; several DE miRNAs between PRLPA and aggressive PA were identified using the GSE46294 miRNA expression profile [17][18]. They suggested that most of

the hub genes were modulated by hsa-miR-489 and hsa-miR-520b via the construction of a miRNA–hub gene network; thus, these two miRNAs may provide new targets for the diagnosis and treatment of PRLPA.

In addition to being downregulated in the PAs' plasma, miR-143 was downregulated in PA tissues, especially in adrenocorticotropic hormone (ACTH)-secreting pituitary tumors [7][8][9]. Although the expression of miR-143 was not associated with the tumor size and postoperative remission rate [9], miR-143 inhibited cell proliferation and promoted apoptosis by targeting K-Ras [8]. Vicchio et al. found that the downregulation of miR-26b-5p and miR-30a-5p was negatively correlated with ki-67, 'atypical' morphological characteristics, and cavernous sinus invasion [19]. These miRNAs can be used as predictors of PA invasion.

In conclusion, exploring the underlying mechanisms between miRNAs and pituitary tumorigenesis may contribute to identifying new potential biomarkers that may be used as an innovative treatment for PA.

3. miRNA in PA-Associated Cell Lines

PA-associated cell lines including mouse (e.g., AtT-20 and GT1.1 cells) and rat (e.g., GH3 and MMQ cells) lines were used for exploring the underlying mechanisms of PA. The expression of miR-143 was downregulated in the GH3 and MMQ cell lines except in the circulation and tissue [7][8][9]. Subsequent experiments revealed that miR-143 inhibited the two cells' proliferation and promoted apoptosis by regulating the oncogene K-Ras [8]. Furthermore, a recent study found that the underexpression of miR-146b-5p was related to the tumor size, the overall survival rate, a poor disease-free survival rate, a poor Knosp grade, and a poor Hardy grade [20]. In addition, miRNA-146b-5p negatively regulated GH3 cell proliferation, invasion, and migration, and induced apoptosis by inhibiting the ephrin receptor A7 (EPHA7) gene via regulating the IRAK4/TRAF6/NF-κB signaling pathway [20].

In murine GT1.1 and AtT-20 cells, the expression of miR-219a-2-3p was significantly downregulated [21]. Moreover, the overexpression of miR-219a-2-3p inhibited cell proliferation and promoted apoptosis as well as reducing MDM2 expression by binding to the 3'-UTR of the MDM2 mRNA and promoting p53 expression [21]. Therefore, miR-219a-2-3p modulated cell proliferation and apoptosis by targeting MDM2/p53 in PA, suggesting that miR-219a-2-3p may be a novel therapeutic marker for PA.

In conclusion, in vitro studies provide greater insight into the pathogenesis of the disease, and the combination of in vitro, in vivo, and clinical specimens (including blood and tissue) will greatly promote the research progress.

4. Exosome-Derived miRNA and PA

In human biological fluids, miRNAs accumulate within extracellular vesicles (EVs, including apoptotic bodies, microvesicles, and exosomes) and bind to macromolecules, such as the AGO2 protein or lipoproteins [22]. Exosomes play a key role in the cells' cross-talk and in the pathogenesis of human diseases.

Recently, the group explored the function of miRNAs in IPAs and the therapeutic strategy of exosome-derived miRNAs for the disease [23]. Twenty DE miRNAs were identified; the two lowest miRNAs, miR-99a-3p and miR-149-5p, were used for the subsequent studies. It was found that exosome-derived miR-99a-3p and miR-149-5p inhibited cell viability, migration, and tube formation [23]. Therefore, it is suggested that the upregulation of miR-99a-3p and miR-149-5p can inhibit the progression of IPA by the exosome, and exosome-derived miRNAs represent good potential candidates for future therapies for IPA.

Acromegaly, an endocrine and metabolic disease caused by GHPAs, is partially attributable to an excessive function of the GH and insulin-like growth factor-1 (IGF1) hormones [24][25][26]. In addition, GHPA-derived exosomes contain miRNAs and proteins that regulate cell proliferation and differentiation in distal extremities. Xiong et al. found that GHPA-derived exosomes may be involved in bone formation and osteoblast proliferation via promoting cell viability and DNA replication [27]. Furthermore, they found that exosome-derived miR-21-5p stimulated osteoblast information in the GH/IGF1 pathway. Taken together, exosome-derived miR-21-5p may be a candidate biomarker for the treatment of acromegaly.

RNA-seq was used for identifying exosome-derived miRNAs in six somatotroph adenomas and six healthy pituitary samples [28]. Herein, a total of 169 DE exosomal miRNAs were identified, and miR-423-5p was significantly downregulated in the somatotroph adenoma, whereas pituitary tumor transforming gene (PTTG1), a target of miR-423-5p, was upregulated in patients and contributed to the promotion of proliferation and migration of somatotropic adenoma cells. Thus, their findings indicate that exosome-derived miRNAs, especially miR-423-5p, may be valuable biomarkers for the development of new therapeutic strategies. Next-generation sequencing showed that miR-26b-5p, miR-126-5p, miR-148b-3p, and miR-150-5p were detected in patients with FSH/LH+ adenoma plasma samples, and also in the exosomes of the patients, but others (i.e., miR-6514-3p, miR-6850-5p, and miR-6867-5p) were not detectable in plasma and exosomes [7]. Interestingly, it is said that the decrease in miR-143-3p in the plasma may be a potential biomarker for patients with FSH/LH+ adenoma after transsphenoidal surgery, but the expression of exosome-derived miR-143-3p in FSH/LH+ samples was not significant, indicating that miR-143-3p is mainly expressed in protein-associated plasma rather than in exosomes.

In conclusion, exosomes are effective markers and promising new therapeutic targets for PA and its complications. However, the role of exosomes, especially intercellular communication, in the pathogenesis of PA needs further investigation.

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