

## The role of microRNAs in the pathogenesis of pituitary tumors

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### 1. ABSTRACT

Pituitary tumors, the most common intracranial tumors, lead to serious morbidity through the inappropriate secretion of pituitary hormones. The anomalous expression of microRNAs (miRNAs), which have a crucial status in the development and function of pituitary gland, promotes the tumorigenesis of hypothalamic–pituitary axis-related pituitary tumors. This mainly leads to alterations in the function of the hypothalamic–pituitary–adrenal axis, hypothalamic–pituitary–gonadal axis and hypothalamic–pituitary–growth hormone. In the tumorigenesis of pituitary tumors, miRNAs have complex roles. They can induce cell cycle arrest, inhibiting cell proliferation and inducing apoptosis via different pathways; however, they also promote the occurrence of pituitary tumors through direct interactions with transcription factors. This review summarizes recent progress in the study of miRNAs on the pathogenesis of pituitary tumors.

### 2. INTRODUCTION

The pituitary gland, or hypophysis, is composed of the anterior pituitary (or adenohypophysis), intermediate lobe and posterior pituitary (or neurohypophysis), and secretes nine hormones that regulate homeostasis. Pituitary adenomas are neuroendocrine, accounting for about 10% of intracranial adenomas, have a prevalence of 22.5%, and are the most frequent intracranial tumors (1). Pituitary adenomas are usually benign and are generated by abnormal individual cells in the pituitary gland that induce changes in endocrine function and metabolism (2). However, the pathogenesis of pituitary tumors is still unclear.

microRNAs (miRNAs) are small, non-coding, single-stranded RNAs that post-transcriptionally regulate the translation and degradation of target mRNAs by binding to partially complementary target sites within the 3' untranslated regions (3'UTR) of select messenger RNAs (3). In pigs, the pituitary gland contains a great number of porcine miRNAs, involved in organ development and function (4). In addition, miRNA profiles in the pituitary change with age (5). miR-26b is crucial in regulating anterior pituitary development (6). In the normal pituitary gland, miR-375 is specifically increased in the intermediate lobe of the mouse pituitary gland (7). The regulation of neurohypophysial hormone may be mediated by miRNAs, as miR-24 regulates both transcript and peptide levels of oxytocin (8). Furthermore, miRNAs may control the active regulation of the hypothalamic–pituitary–thyroid axis (9). The miRNAs in POMC neurons are also crucial in pituitary dysfunction and neurodegeneration (10). Thus, miRNAs, including their corresponding target sites, participate in both normal functions and dysfunctions of the pituitary gland (11,12).

miRNAs are associated with various cancers; for example, miR-125b is associated with hepatocellular carcinoma, miR-21 is associated with leukemia, miR-16 is associated with chronic lymphocytic leukemia, and miR-192 is associated with pituitary adenomas (13). Among the 30 miRNAs differentially expressed between the normal pituitary gland and pituitary adenomas, 24 miRNAs were identified as predictors of pituitary adenoma occurrence and 29 miRNAs could predict the histype of the adenoma (14), further demonstrating that miRNAs may play a key role in pituitary tumorigenesis.

In this review, we discuss the role of miRNAs in the pathogenesis of pituitary tumors.

### 3. MICRORNAS IN THE DEVELOPMENT OF PITUITARY TUMORS

#### 3.1. Hypothalamic–pituitary–adrenal axis

The hypothalamic–pituitary–adrenal (HPA) axis constitutes the major neuroendocrine system and controls stress and many physiological processes such as digestion, the immune system, mood and emotions, sexuality, and energy storage and expenditure. In rat anterior pituitary cells, the up-regulation of ob miR-325-3p promotes the stress-induced suppression of luteinizing hormone secretion (15), suggesting miRNAs are involved in stress-related systems. Moreover, miR-449a, found in rat anterior pituitary cells, promotes the stress-induced, glucocorticoid-mediated down-regulation of CRF type 1 receptor expression (16). Recent studies based on a murine model reported that paternal stress exposure could change sperm miRNAs, leading to a reprogramming of HPA stress axis regulation in offspring (17), further demonstrating the crucial role of miRNAs in the HPA axis.

Adrenocorticotrophic hormone (ACTH) is a polypeptide tropic hormone produced and secreted by the anterior pituitary gland in response to biological stress. ACTH stimulates the secretion of glucocorticoid steroid hormones from adrenal cortex cells by binding to cell surface ACTH receptors. ACTH-secreting pituitary tumors are the most common secretory subtype to undergo malignant transformation (18,19). The majority of ACTH-secreting pituitary tumors present with clinical and biochemical features of Cushing's syndrome (19), characterized by excess cortisol in the blood and many physiological consequences including centripetal obesity, impaired immune response, generalized muscle weakness, menstrual irregularities, hypertension and premature death secondary to cardiovascular disease, infection, or suicide (20,21). In ACTH-secreting pituitary tumors, miRNAs are expressed differently. The miR-145, miR-21, miR-141, let-7a, miR-150, miR-15a, miR-16 and miR-143 are down-regulated in ACTH-secreting pituitary tumors (22), while miR-122 and miR-493 are up-regulated (23). These findings suggest a role of miRNAs in the corticotrophic tumorigenesis.

The miRNA lethal-7 (let-7) was one of the first two miRNAs identified in the nematode as a key developmental regulator highly conserved across species (24). During mouse pituitary development, let7b/c can down-regulate the expression of RNA-binding protein KSRP by directly binding to the 3'UTR, resulting in the up-regulation of the hormone alpha-GSU (alpha glycoprotein subunit, common to three pituitary hormones) (25). In pituitary adenomas, the loss of let-7 can up-regulate the expression of high-mobility group A2, which is typically increased during embryogenesis and

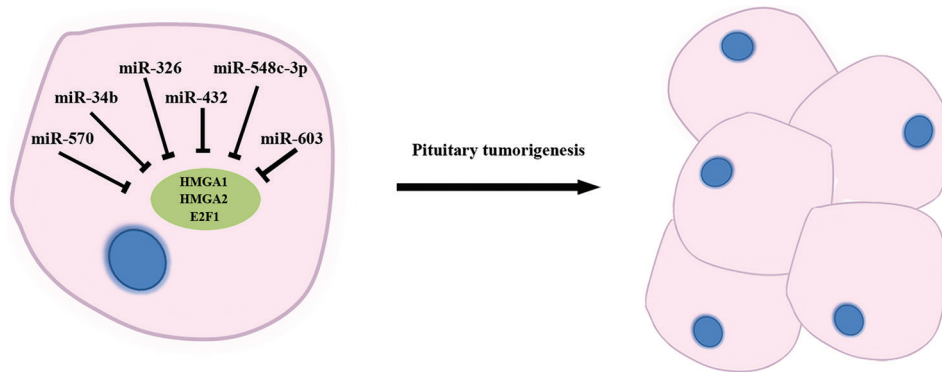
in various tumors (26), suggesting the potential role of let-7 in pituitary tumorigenesis and progression. In ACTH-secreting pituitary adenomas, miR-26 delays the cell cycle in G1 phase by regulating protein kinase Cdelta, which is involved in the cyclin E and cyclin A pathways (27).

#### 3.2. Hypothalamic–pituitary–gonadal axis

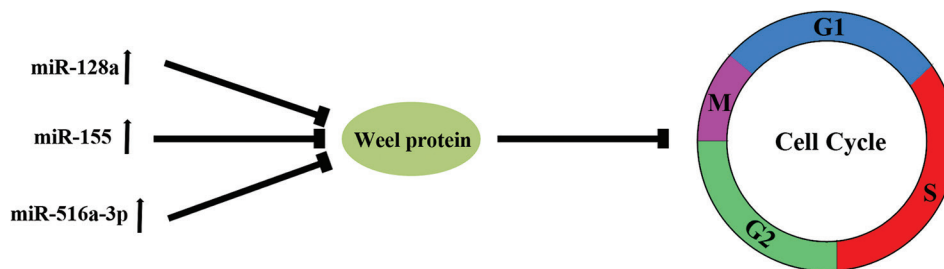
The hypothalamic–pituitary–gonadal (HPG) axis plays a crucial role in the reproductive and immune systems. The hypothalamus produces gonadotropin-releasing hormone (GnRH). The anterior portion of the pituitary gland produces luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and the gonads produce estrogen and testosterone. The microRNAs miR-130a, miR-199b-3p, miR-200b and miR-125b are down-regulated in prolactinomas compared to the normal anterior pituitary gland, while miR-342-3p, miR-432, miR-23b, miR-493, miR-493 and miR-664 are up-regulated (28). In addition, miR-132 and miR-212 regulate the GnRH-stimulated biosynthetic process (29). Both miR-132 and miR-212 are induced by gonadotropin-releasing hormone, resulting in the regulation of cellular morphology and migration by targeting the p250Rho GTPase activating protein in LbetaT2 pituitary gonadotrope cells (30). The study based on female mice showed that both miR-200b and miR-429 increased in expression in the pituitary gland, leading to the suppression of the transcriptional repressor ZEB1 (31). An *in vitro* study with a pig pituitary cell model showed that miR-361-3p may inhibit FSH secretion (32). All these findings suggest a role of miRNAs in the function of the HPG axis. However, there are few study reports regarding the precise role of miRNAs in hormone-related pituitary tumors.

#### 3.3. Hypothalamic–pituitary–growth hormone

The arcuate nucleus of the hypothalamus releases growth-hormone-releasing hormone (GHRH), a releasing hormone for growth hormone (GH). GH, secreted by the anterior pituitary gland, stimulates cell reproduction and regeneration, resulting in growth in humans. The GH-secreting pituitary adenoma shows a male-dominant tendency (33), while excessive GH secretion can cause gigantism in juveniles or acromegaly in adults (34). The miRNAs in GH-secreting pituitary adenomas have been analyzed, and several miRNAs were found differentially expressed in GH-secreting pituitary adenomas and normal pituitaries (35). Moreover, compared with micro-adenomas, human macro-adenomas showed an up-regulation of miR-184, miR-524-5p, miR-629 and miR-766, and a down-regulation of miR-124, miR-222, miR-32, miR-744 and miR-765 (35). More down-regulated miRNAs in human pituitary GH adenomas, including miR-34b, miR-326, miR-432, miR-548c-3p, miR-570 and miR-603, were later reported to target the high-mobility group A1 (HMGA1), HMGA2 and E2F1 genes, leading to the



**Figure 1.** microRNAs (miRNAs) in the tumorigenesis of growth hormone-secreting pituitary adenomas. In the tumorigenesis of growth hormone-secreting pituitary adenomas, miR-34b, miR-326, miR-432, miR-548c-3p, miR-570 and miR-603 are down-regulated, which target in genes high-mobility group A1 (HMG A1), HMG A2 and E2F1, leading to the promotion of pituitary tumorigenesis.



**Figure 2.** microRNAs (miRNAs) regulate tumor suppressor Wee1 in pituitary tumor. The overexpression of miR-128a, miR-155 and miR-516a-3p can inhibit the expression of tumor suppressor Wee1 protein, resulting in the cell entering into mitosis at the G2/M checkpoint.

promotion of pituitary tumorigenesis (36) (Figure 1). Among several down-regulated miRNAs in pituitary macro-adenomas, the down-regulation of miR-15 and miR-16 is associated with a larger tumor size and a lower p43 secretion, which can regulate the local inflammatory response and provide anti-neoplastic properties (37).

#### 4. THE ROLE OF MICRORNAS IN TUMOR PROLIFERATION

Importantly, miRNAs are involved in the targeting of cell cycle genes during tumor growth. In the rat pituitary adenoma cell line GH3HMG A, miRNAs inhibit cell proliferation (38). In GH-secreting pituitary tumors, miR-26b and miR-128 play a central regulatory role in tumor growth via the PTEN-AKT pathway (a cell cycle regulation pathway), which has been demonstrated in xenografts (39). Furthermore, decreased miR-26b and increased miR-128 was found to suppress tumor growth (39).

Studies on miRNAs in tumor proliferation usually focus on their role in the tumor suppression of non-functional pituitary adenomas. In the tumorigenesis of non-functioning pituitary adenomas (NFAs), miR-135a,

miR-140-5p, miR-582-3p, miR-582-5p and miR-938 target Smad3, leading to the down-regulation of the TGF-beta signaling pathway. Furthermore, the overexpression of these miRNAs is associated with tumor size (40). The maternally expressed gene 3 (MEG3) is selectively lost in NFAs of gonadotroph origin. Cheunsuchon *et al.* (41) found that 13 miRNAs at the DLK1-MEG3 locus were down-regulated in human NFAs, among which the down-regulation in miR-134 induced cell cycle arrest at the G2/M phase in PDFS cells derived from a human NFA. In addition, the exogenous overexpression of miR-128a, miR-155 and miR-516a-3p can inhibit the expression of Wee1 protein (44), a tumor suppressor that prevents mitotic entry at the G2/M checkpoint (42, 43) (Figure 2). Another miRNA, miR-107, acts as tumor suppressor by inhibiting cell proliferation (45). In addition, miR-200c plays a crucial role in inducing the apoptosis of pituitary tumor cells (46).

Transcription factors participate in pituitary tumorigenesis through multiple mechanisms, such as initiating tumor neovascularization (47) and reducing cellular viability (48). The miRNAs have been found to play a crucial role through interacting with transcription factors in several tumors, such as breast cancer (49), hepatocellular carcinoma (50), neuroblastoma (51) and

colorectal cancer (52). Gong and colleagues (53) found a complex interaction between miRNAs, transcription factors and genes may promote the occurrence of pituitary adenomas. However, the precise mechanism behind this interaction is still unclear.

## 5. CONCLUSION

The normal regulation of miRNAs is crucial for the normal development and physiological function of the pituitary gland. The major function of the pituitary is carried out through hypothalamic–pituitary axes, especially the hypothalamic–pituitary–adrenal axis, and hypothalamic–pituitary–gonadal axis and hypothalamic–pituitary–growth hormone. The anomalous expression of miRNAs promotes the tumorigenesis of functional pituitary tumors through different pathways and mechanisms: they can induce cell cycle arrest, inhibit cell proliferation and induce apoptosis. miRNAs also promote the occurrence of pituitary tumors through direct interactions with transcription factors. A further understanding on the relationship between miRNAs and pituitary tumorigenesis may provide novel therapeutic targets. Thus, future work based on pituitary tumor cell lines *in vitro* and animal models *in vivo* may provide more knowledge on the molecular mechanisms of pituitary tumor pathogenesis and the development of novel therapeutic strategies.

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**Abbreviations:** miRNAs, microRNAs; 3'UTR, 3' untranslated regions; HPA, hypothalamic–pituitary–adrenal; ACTH, Adrenocorticotrophic hormone; HPG, hypothalamic–pituitary–gonadal; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GHRH, growth-hormone-releasing hormone; HMGA1, high-mobility group A1; NFAs, non-functioning pituitary adenomas; MEG3, maternally expressed gene 3

**Key Words:** MicroRNAs, Adrenocorticotrophic hormone, Let-7, Review

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