The Role of Long Noncoding RNAs in the Biology of Pituitary Adenomas

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Key words
- Biomarker
- lncRNAs
- Pathogenesis
- Pituitary adenoma
- Therapeutic targets

Abbreviations and Acronyms
ESRP2: Epithelial splicing regulatory protein 2
FPA: Nonfunctioning pituitary adenoma
GH: Growth hormone
HOTAIR: HOX transcript antisense RNA
lncRNA: Long noncoding RNA
miRNA: microRNA
mRNA: Messenger RNA
PVT1: Plasmacytoma variant translocation 1

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Long noncoding RNAs (lncRNAs) are a large group of noncoding RNAs 200 nucleotides long. lncRNAs that function as regulatory factors have been identified for several complex cellular processes, such as cell death, growth, differentiation, apoptosis, epigenetic regulation, and so on. Many lncRNAs have altered expression and are likely to play a functional role in oncogenesis. The pituitary adenoma is the second most common intracranial tumor. Despite this situation, the molecular mechanism of pituitary adenoma formation has not yet been fully identified. This review summarizes recent progress in the study of lncRNAs on the pathogenesis of pituitary tumors. We cover the latest results associated with this role and highlight the therapeutic possibilities for pituitary adenomas.

INTRODUCTION

The pituitary gland, or hypophysis, is composed of the anterior pituitary (or adenohypophysis), intermediate lobe, and posterior pituitary (or neurohypophysis) and secretes 9 hormones that regulate homeostasis. The posterior pituitary, the nervous part, is a projection of the hypothalamus that stores but does not produce hormones such as oxytocin and vasopressin. The anterior pituitary is composed of 5 endocrine cell types that specifically produce different hormones such as growth hormone (GH), prolactin, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, and adrenocorticotropic hormone. Those hormones influence growth, metabolism, and reproduction, highlighting the complexity of the functional study of this gland. 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] They are divided into 2 subgroups: macroadenomas (>1 cm) and microadenomas (<1 cm). 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] Some of these neoplasms are locally invasive. Only a small part (0.1%–0.2%) also shows signs of malignancy. However, the pathogenesis of pituitary tumors is still unclear.

Long noncoding RNAs (lncRNAs) are a class of noncoding RNAs that are longer than 200 nucleotides and lack the protein-coding potential.[3] Recently, Iyer et al. reported that there are about 60,000 noncoding RNAs in the human genome and >70% of these are lncRNAs.[4] About 80% of lncRNAs are not annotated. lncRNAs can regulate biological processes via diverse molecular mechanisms, such as decoys, scaffold, signal transducer, sponges for microRNAs (miRNAs), and a guide for chromatin modifiers.[5,6] Many lncRNAs regulate the expression of protein-coding genes via in cis (affecting neighboring genes) or in trans (affecting distant genes on different chromosomes) mechanisms.[7,8] Various lncRNAs have been reported to regulate individual genes and gene expression programs through epigenetic regulation or by altering the basal transcriptional machinery. Specifically, lncRNAs can 1) regulate the transcription of downstream genes; 2) regulate messenger RNA (mRNA) splicing patterns and produce different splice variants; 3) modulate activity of proteins; 4) scaffolds for assembly of multiple component complexes; 5) regulate subcellular localization of proteins; and 6) function as transcriptional precursors of small RNAs.[9] It is conceivable that aberrant expression of lncRNAs results in dysregulation of normal biological and pathologic processes and thereby contributes to the pathogenesis of disease.[10] Using a comparative mammalian genomics approach coupled with evolutionary analysis, Khachane and Harrison identified a small population of conserved lncRNAs in the evolution and proposed that these lncRNAs could play an important role in tumorigenesis.[11] In this review, we discuss the role of lncRNAs in the pathogenesis of pituitary adenomas and consider them as promising therapeutic targets in the future (Table 1).

lncRNA

lncRNAs are transcripts of >200 nucleotides that do not encode proteins. Although this definition is given arbitrarily, it distinguishes lncRNAs from

Table 1. Long Noncoding RNAs Involved in the Pathogenesis of Pituitary Adenoma

Long Noncoding RNA	Gene Target	Type of Pituitary Adenoma	Biological Function	Expression	Reference
MEG3	/	Invasive NFPA	Tumor suppressor	Downregulation	Li et al. 2015[12]
HOTAIR	/	Invasive NFPA	Tumor cell activation of invasive properties and development tumor	Upregulation	Li et al., 2015[12]
H19	mTOR/4E-BP1	PRL, GH, ACTH, FSH	Inhibits tumor cell proliferation and tumor growth	Upregulation	Wu et al., 2018[13]
RPSAP52	HMGA1 and HMGA2	FSH/LH	Promotes cell growth by enhancing the G1-S transition of the cell cycle	Upregulation	D'Angelo, et al., 2019[14]
IFNG-AS1	ESRP2	NFPA	Promotes cell proliferation, invasion, migration, and inhibiting apoptosis	Upregulation	Lu et al., 2018[15]
CCAT2	PTTG1, E2F1	NFPA	Promotes cell proliferation, invasion, migration, and invasion	Upregulation	Fu et al., 2018[16]
C5orf66-AS1	PITX1	Invasive pituitary adenoma	Tumor cell activation of invasive properties	Downregulation	Yu et al., 2017[17]
MEG3	p53	NFPA	Suppresses tumor growth	Downregulation	Chunharojrith et al., 2015[18]
MEG3	/	NFPA	Tumor suppressor	Downregulation	Zhao et al., 2005[19]; Zhang et al., 2003[20]; Mezzomo et al., 2012[21]
MEG3	/	ACTH, GH, PRL	Development tumor	Upregulation	Mezzomo et al., 2012[21]
PVT1	Wnt/β-catenin	Invasive GH	Enhanced proliferation, migration, and EMT	Upregulation	Zhang et al., 2019[22]
HULC	PI3K/AKT/mTOR and JAK1/STAT3	PRL, GH	Promote tumor cells viability, migration, invasion, and hormone secretion	Upregulation	Rui et al., 2019[23]
H19	IGF-1	Invasive GH	Tumor cell activation of invasive properties	Upregulation	Wang et al., 2018[24]
SNHG1	TGF/SMAD, RAB11A/Wnt/β-catenin	Invasive (GH, FSH/LH, PRL, ACTH)	Promotes tumor cell proliferation, migration, invasion, and EMT	Upregulation	Lu et al., 2018[25]

/, not mentioned in the article; NFPA, nonfunctioning pituitary adenoma; HOTAIR, HOX transcript antisense RNA; mTOR, mammalian target of rapamycin; PRL, prolactin; GH, growth hormone; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; IFNG-AS1, IFNG antisense RNA 1; CCAT2, colon cancer-associated transcript 2; PVT1, plasmacytoma variant translocation 1; EMT, epithelial—mesenchymal transition; HULC, highly upregulated in liver cancer; PI3K, phosphatidylinositol-3-kinase; IGF-1, insulinlike growth factor 1; TGF, transforming growth factor.

small regulatory RNAs such as miRNAs, piwi-interacting RNAs, and other small nuclear RNAs. lncRNAs, usually transcribed by RNA polymerase II, make up a heterogeneous group, some of which can extend to several tens of kb. lncRNA genes have several common characteristics with genes encoding proteins, such as epigenetic profiles, the presence of splicing, and polyadenylation signals, as well as the size of exons and introns.[26] However, compared with mRNA, lncRNAs are more enriched in the nucleus and show the lowest sequence conservation, although some are highly conserved.[26] In addition, lncRNA genes express themselves weaker than the coding genes, and their expression is particularly specific for certain tissues. Depending on their position relative to the coding genes, lncRNA can be divided into 2 broad categories: intergenic lncRNAs and intragenic lncRNAs. Intergenic lncRNAs localized by definition in unannotated regions of the genome are commonly referred to as lincRNA. They represent the most studied class of lncRNA.[26] On the other hand, intragenic lncRNAs can be subdivided depending on how they overlap the coding genes or their orientation in relation to them (e.g., antisense and intron). Many of the intergenic lncRNAs have a transcription initiation site close to the coding gene site, with transcription located on the opposite chain (divergent transcription). It has recently been shown that genes associated with these divergent transcripts often encode transcription regulators involved in cell development and differentiation.[27] Some lncRNAs overlap with small RNAs, such as small nuclear RNAs or miRNAs, with potential functional bonds, as in the case of regions with an imprinted genome. Many lncRNAs contain repeating elements, such as long disseminated nuclear elements or short disseminated nuclear elements, with potential functional consequences.[28,29] However, lncRNAs do not have a conserved sequence or structure that may indicate a specific function.[26] As a result, most studies aimed at identifying potentially relevant lncRNAs in a given physiologic or pathologic context are based on coexpression or joint regulatory analysis. The function of neighboring genes having a profile similar to lncRNA (the function of which must be determined) is then transposed.[30]

THE ROLE OF lncRNAs IN DISEASE DEVELOPMENT

Given their contribution to physiologic processes, a change in the expression level of lncRNAs can lead to the development of diseases such as cancer. Many studies showing a lack of regulation of lncRNAs in various types of cancer cells have suggested that lncRNAs may act as tumor suppressors or potential oncogenes.[31] Among the cancer-related lncRNA examples, the role of HOTAIR (HOX transcript antisense RNA) has been the most studied. Several studies have reported overexpression of HOTAIR in various forms of cancer, in which it is sometimes involved in the formation of metastases.[32,33] MALAT1 is another well-studied lncRNA; its overexpression is associated with the metastatic state of tumors. It has been proposed to use it as a prognostic marker for lung cancer.[31] Similarly, oncogenic functions have been proposed for some other lncRNAs, for example, liver cancer (HULC), prostate cancer (PCA3), and kidney (MVIH).[34-36] Some lncRNAs, such as LincRNA-p21 and MEG3, were involved in modulating the p53 response.[37,38] The involvement of lncRNA in the development of diseases is not limited to cancer. The number of studies suggesting the involvement of lncRNA in the development of various diseases continues to increase.[31] CDKN2B-as1 (ANRIL), an lncRNA involved in several types of cancer, is also associated with atherosclerosis.[39-41] Similarly, the development of various diseases (e.g., Alzheimer disease and neonatal diabetes) may result from deregulation of lncRNA expression. In addition to deregulating lncRNA expression, several genetic studies have shown the presence of mutations in their primary sequences.[31,42]

THE ROLE OF lncRNAs IN ONCOGENESIS OF PITUITARY ADENOMAS

More and more oncogenes (GNAS, PI3KCA, PTTG), tumor suppressor genes (GADD45γ, AIP, MEN1, PRKAR1A, Reprimo), structural proteins (Magmas), and epigenetic modifications of some genes (FGFR2, MEGE-A, MEG3) are associated with the development and progression of the pituitary adenoma.[43] For example, in 1 study, scientists from China performed a genomic analysis of lncRNAs and mRNA, which were obtained from samples of patients with gonadotropin adenoma and healthy pituitary tissue using RNA-seq.[44] These investigators created a unique coexpression subnet including 186 lncRNAs that interact with 15 major coding genes of the mammalian target of rapamycin pathway, which can contribute to tumor pathogenesis. For example, Li et al.[12] from the Beijing Neurosurgical Institute showed that the change in the expression of lncRNAs MEG3 and HOTAIR is associated with the development and invasion of nonfunctioning pituitary adenomas (NFPA). Zhang et al.[45] reported that exosomal H19 has been shown to inhibit the growth of tumor cells in the distal pituitary gland by inhibiting 4E-BP1 phosphorylation. Plasma exosomal H19 serves as a prognostic biomarker for a drug response in patients with prolactinomas. In general, H19 expression is negatively correlated with the progression of the pituitary adenoma. Accordingly, an increase in H19 expression inhibits pituitary tumor cell proliferation in vitro and tumor growth in vivo. Wu et al.[13] reported that H19 function controls tumor growth by inhibiting mTORC1 function. These investigators showed that H19 is more effective than cabergoline treatment. Their study proved the role of the H19-mTOR-4E-BP1 axis in the regulation of pituitary tumor growth, which will become a potential therapeutic target for pituitary tumors. D'Angelo et al.[14] reported that overexpression of lncRNA RPSAP52 promotes pituitary oncogenesis. These investigators suggested that lncRNA RPSAP52 is a new player in the development of pituitary adenomas. Lu et al.[15] showed that epithelial splicing regulatory protein 2 (ESRP2) is the target protein of lncRNA IFNG-AS1 in pituitary adenomas; knockdown ESRP2 reawakened the main effect of lncRNA IFNG-AS1 knockdown-inhibition of tumor growth. Overexpression of ESRP2 eliminated the tumor-stimulating effects of overexpression of IFNG-AS1 in HP75 cells. The results of these scientists showed that IFNG-AS1 functions as an oncogene in pituitary adenoma, interacting with ESRP2. Fu et al.[16] proved that CCAT2 behaves like an oncogene in pituitary adenomas. Overexpression of CCAT2 promotes carcinogenesis and the development of pituitary adenoma. Yu et al.[17] proved that C5orf66-AS1 inhibits the development and invasion of pituitary adenomas. It has been proved that GADD45γ, MEG3, and P8 are involved in the pathogenesis of nonfunctional and corticotrophic pituitary tumors.[46] Scientists from Germany[18-20] analyzed their expression in various normal human tissues and in tumors of various types of the pituitary gland and investigated the GADD45γ mutations in the subgroup of adenomas. Absolute quantification using real-time reverse transcription polymerase chain reaction (qRT-PCR) was used in this study. One of the main conclusions of the researchers is that MEG3 is a suppressor of pituitary tumors, and its inactivation contributes to the development of NFPA. Mezzomo et al.[21] confirmed that MEG3 expression is lost or reduced in NFPA. However, they noted a high level of MEG3 expression in the functional pituitary adenomas. The 2 groups of tumors are probably genetically different and may have a different natural history.

Plasmacytoma variant translocation 1 (PVT1) plays an oncogenic role in pituitary adenoma cells, activating Wnt/β-catenin (the canonical Wnt pathway) signaling.[22] Cell proliferation and migration were inhibited when the PVT1 gene was destroyed. Scientists have proved that knockdown PVT1 inhibits the migration and epithelial–mesenchymal transition of pituitary adenoma cells. Decreased regulation of PVT1 blocks the activity of the Wnt/β-catenin signaling pathway. PVT1 provokes the development of the pituitary adenoma by including the Wnt/β-catenin signaling pathway.

FUTURE PROSPECTS

A promising diagnostic approach for many tumors is a liquid biopsy, which involves finding and measuring the level of various circulating biomolecules in human body fluids (e.g., blood, urine, or saliva). Most lncRNAs are expressed within the cells themselves. However, in many biological fluids of the human body (e.g., blood), numerous lncRNAs, called circulating lncRNAs, have been detected. Circulating lncRNAs can be found in various forms: enclosed in exosomes or associated with

proteins. These lncRNAs are resistant to nucleases, which makes them attractive as potential biomarkers for the diagnosis, prognosis, and monitoring of therapy. The expression profile of circulating lncRNAs changes significantly under various pathologic conditions in humans, including pituitary adenomas (e.g., in blood samples of patients with hepatocellular carcinoma [HULC]).[47] In several studies, the detection of PCA3 (prostate cancer gene 3) in urine is described as a more sensitive biomarker compared with the prostate-specific antigen.[48] The detection of some lncRNAs in tissue is predictive. For example, in hepatocellular carcinoma, increased expression of MALAT1 is associated with a poor prognosis and decreased survival after liver transplantation.[49] Based on the data on MEG3, a known suppressor of pituitary tumors, we believe that preparations based on lncRNA MEG3 can be used to inhibit the growth of NFPA. We also believe that a change in the expression of PVT1 (i.e., a significant increase in the tissues of the pituitary adenoma and cancer cells relative to healthy tissue) may serve as a therapeutic target for the treatment of pituitary adenomas. Rui et al.[23] reported that HULC had a higher expression level in secreting pituitary adenoma GH3 cells. Overexpression of HULC significantly promoted the viability, migration, invasion, and hormone secretion of GH3 cells. However, knockdown of HULC had opposite effects and induced GH3 cell apoptosis. That study contributes to the further understanding of the pathogenesis of secreting pituitary adenomas and is helpful for defining potential diagnostic and therapeutic targets. Lu et al.[24] in their study argued that lncRNA H19 might be a target for the study of GH-secreting pituitary adenoma invasion and a potential index for the diagnosis or prognosis of this tumor. Wang et al.[25] reported upregulation of lncRNA SNHG1 in invasive pituitary tumor tissues and cell lines. These investigators found that lncRNA SNHG1 played an oncogenic role in pituitary tumor progression by activating the RAB11A (Ras-related protein Rab-11A)/Wnt/β-catenin and TGF-β (transforming growth factor β)/SMAD3 signaling pathways. These data suggest that lncRNA SNHG1 promotes the progression of pituitary tumors and is a potential therapeutic target for invasive pituitary tumor. Although we are just beginning to study the biology of lncRNAs, and there are many more questions that need to be clarified, it is possible that in the future they may become a therapeutic target for pituitary adenomas based on their significance in tumor biology.

CONCLUSIONS

lncRNAs are important regulators of gene expression and perform key physiologic functions in many tissues, including the pituitary gland. lncRNAs are also involved in the genesis of pituitary adenoma. The scientific community has made great strides by identifying several lncRNAs with altered expression in pituitary tumors. Because tumors of the anterior pituitary gland show different behavior depending on the histotype, it would be advisable to classify lncRNAs as belonging to a particular class of tumors. Their expression is specific for various histotypes and may correlate with tumor size and other clinical and pathologic signs. Despite the availability of reliable evidence that lncRNAs are involved in the tumor process of the pituitary gland, specific mechanisms for their participation are little known. Modern molecular biological studies are aimed at determining targets for individual lncRNAs and their clusters, which, of course, will allow further tuning of signaling pathways, the disturbances of which are associated with a specific disease. These advances will allow us to manipulate the functions of lncRNAs for future use as therapeutic targets.

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