Noncoding RNAs in Endocrine Malignancy

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ABSTRACT

Only recently has it been uncovered that the mammalian transcriptome includes a large number of noncoding RNAs (ncRNAs) that play a variety of important regulatory roles in gene expression and other biological processes. Among numerous kinds of ncRNAs, short noncoding RNAs, such as microRNAs, have been extensively investigated with regard to their biogenesis, function, and importance in carcinogenesis. Long noncoding RNAs (lncRNAs) have only recently been implicated in playing a key regulatory role in cancer biology. The deregulation of ncRNAs has been demonstrated to have important roles in the regulation and progression of cancer

development. In this review, we describe the roles of both short noncoding RNAs (including microRNAs, small nuclear RNAs, and piwi-interacting RNAs) and lncRNAs in carcinogenesis and outline the possible underlying genetic mechanisms, with particular emphasis on clinical applications. The focus of our review includes studies from the literature on ncRNAs in traditional endocrine-related cancers, including thyroid, parathyroid, adrenal gland, and gastrointestinal neuroendocrine malignancies. The current and potential future applications of ncRNAs in clinical cancer research is also discussed, with emphasis on diagnosis and future treatment. *The Oncologist* 2014;19:483–491

Implications for Practice: Our knowledge of noncoding RNA (ncRNA) has boomed since the turn of the century, and progressive research in this field now aims to take advantage of our improved understanding of these key regulators. Present preclinical evidence in relation to endocrine malignancy has great potential to transform future management of a unique group of diseases that have failed to respond to conventional treatment. Epigenetic ncRNA regulation is clearly of great importance and should be harnessed in the future as a means of not only enhancing our understanding of endocrine malignancy but also, ultimately, of translating current knowledge into therapeutic success.

INTRODUCTION

The discovery that more than 95% of human transcriptional output is noncoding RNA (ncRNA) [1] raised questions about the traditional opinion in molecular biology that RNA is only a simple intermediary between DNA and protein. An ncRNA is, by definition, an RNA that does not transcribe for a protein, and there is presently an increasing number of well-characterized ncRNAs that are of evolving scientific and clinical interest [2]. It is now evident that ncRNAs play important functional and structural roles in both health and disease [3, 4]. Progressive research in this field aims to take advantage of our improved understanding of these key regulators to ultimately translate this knowledge into improved diagnostic, prognostic, and therapeutic options in oncology. This review summarizes the evidence to date and demonstrates the burgeoning potential of ncRNA-driven scientific and clinical research [5]

Our knowledge of ncRNAs has boomed since the turn of the century, and a myriad of ncRNAs have now been characterized and can be broadly classified based on size [6]. Small noncoding RNAs (sncRNAs) are typically 18–200 nucleotides in length compared with long ncRNAs (lncRNAs), which can range from

200 nucleotides to more than 100 kilobase pairs. More specifically, sncRNAs are of vital importance to fundamental biological processes and, therefore, can contribute significantly to certain pathophysiological states. The most well-known families of sncRNAs are microRNAs (miRNAs) and small interfering RNAs, both of which have established roles in RNA interference [1, 7, 8]. Other sncRNA families include small nucleolar RNAs (snoRNAs), small nuclear RNAs, and piwi-interacting RNAs. Detailed descriptions of sncRNA biogenesis and function have been described previously [8–10].

For the purposes of this review, microRNAs will be the primary focus; however, additional ncRNAs of note will be discussed briefly to highlight their growing potential and our current understanding of the roles they play in cancer.

SMALL NONCODING RNA

MicroRNAs

miRNAs are endogenous, single-stranded, short RNA sequences (~22 nucleotides) that regulate gene expression at the

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post-transcriptional level by base pairing with target mRNA sequences. miRNA-mediated gene silencing is generally accomplished by imperfect base pairing of 5' regions of miRNAs with the target mRNA sequence, leading to translational repression and/or mRNA degradation [8, 11–13]. Thousands of human miRNAs have now been characterized. They are known to play important roles in a wide variety of processes including growth, differentiation, immune reactions, and adaptation to physiological stress [1, 3, 7, 8, 10, 14, 15]. Given that a single miRNA can target hundreds of mRNAs and a single mRNA can be targeted by multiple miRNAs [16], they are attractive therapeutic targets in disease, particularly cancer [16, 17]. Of additional importance is the fact that miRNAs are stable in the circulation and, therefore, may be used as serum biomarkers [18, 19]. From a translational viewpoint, patterns of differential miRNA expression have been shown to be of diagnostic and prognostic utility in a multitude of cancers and are now on the cusp of clinical application (Tables 1–3).

Small Nucleolar RNA and Piwi-Interacting RNA

Small nucleolar RNAs (snoRNAs) and small nuclear RNAs are best known as guide molecules for site-specific methylation and pseudouridylation of other RNAs [8]. As their name implies, they are typically localized to the nucleolus or nucleus, respectively, where they play important roles in the modification and processing of ribosomal RNA. Certain snoRNAs have been shown to influence mRNA splicing and may even serve as miRNA precursors [8].

With regard to human disease, deletion of the snoRNA cluster SNORD116 C/D box is a paternally inherited deletion evident in Prader-Willi syndrome [19]. In addition, various snoRNAs are differentially expressed in non-small cell lung cancer [20], peripheral T-cell lymphoma [21], and prostate cancer [22]. Other studies have shown that a homozygous deletion of the snoRNA U50 is associated with prostate cancer development [23] and undergoes frequent deletion and transcriptional downregulation in breast cancer [24].

Of additional interest is the well-known small nuclear RNA 7SK (also known as RN7SK), which regulates transcription by inhibiting the activity of *CDK9/cyclin T1* complexes [25]. *HMGAI* has been identified as a novel RN7SK interaction gene and is often overexpressed in human malignancies, including thyroid cancer [26]. Intriguingly, RN7SK has also been shown to regulate expression of *LARP7*, leading to a novel syndrome of facial dysmorphism, dwarfism, and intellectual disability [27]. Although the precise mechanism by which this group of small RNAs contributes carcinogenesis is still unknown, it is likely that such disease associations reflect underlying mechanistic importance.

LONG NONCODING RNAs

Long noncoding RNAs can be defined as RNA molecules greater than 200 nt in length [28] and can be divided into five subclasses depending on their genomic location (intronic or intergenic). They are generally involved in regulating genetic expression at various levels, including chromatin modification, transcription, and post-transcriptional processing, such as mRNA splicing and translation [12]. Given such intrinsic involvement, it is no surprise that they are now known to be of importance in a number of biological processes and

pathological disease states [1, 10, 29]. Altered expression in cancer has recently been revealed [30, 31].

One defined mechanism of lncRNA action involves interaction with chromatin remodeling complexes, which are of known importance in carcinogenesis. The lncRNA ANRIL (antisense noncoding RNA in the *INK4* locus), for example, has been shown to be altered in up to 30%–40% of human tumors [6]. This may relate to associations with three tumor-suppressor genes that are often deleted in this context [32]. Another example of a chromatin-modifying lncRNA is HOTAIR (HOX antisense intergenic RNA) [7]. Gupta et al. [33] found that HOTAIR expression is significantly upregulated in both primary and metastatic breast cancer (up to 2,000-fold compared with normal breast tissue); with regard to outcome associations, they also showed that expression positively correlated with metastasis and worse survival outcomes. HOTAIR has since been shown to promote metastasis by heightening the invasiveness of breast cancer cells by altering the expression of *polycomb repressive complex 2*, which reprograms the global chromatin state of tumor cells [34].

The advent of high-throughput gene-sequencing technologies has led to the recent discovery of a variety of novel lncRNAs. LSTINCT5 is an intergenic lncRNA identified by Silva et al. [35] that is overexpressed in breast and ovarian cancer cell lines. Functional importance was demonstrated through knockdown experiments that resulted in decreased proliferation in both cell lines [35]. Similarly, Prensner et al. [36] identified an lncRNA, later named PCAT1, that was selectively upregulated only in prostate cancer. Similar to HOTAIR, PCAT1 functions predominantly as a transcriptional repressor by facilitating transregulation of genes preferentially involved in mitosis and cell division, including known tumor suppressor genes such as *BRCA2* [28]. Another novel lncRNA, prostate cancer noncoding RNA 1 (PCNCR1), was identified in a “gene desert” on chromosome 8q24.2 and is associated with susceptibility to prostate cancer [37]. The lncRNA differential display code 3 (DD3) is also highly overexpressed in prostate cancer, yet little is known about the role DD3 may play in prostate cancer progression [38]. DD3 has been developed into a highly specific, nucleic acid amplification-based marker of prostate cancer that demonstrated higher specificity than serum prostate-specific antigen [39, 40]. The rapid timeline of novel lncRNA discoveries suggests that their clinical utility in medicinal applications is only beginning [6].

Of additional interest is steroid receptor RNA activator (SRA), which was the first lncRNA shown to function as a gene regulator. SRA is overexpressed in breast, uterine, and ovarian tumors and increases cell proliferation in certain hormone-dependent breast cancers [41, 42] and prostate cancers [43]. BC200 (also known as BCYRN1) is also greatly upregulated in ovarian cancer [44] and is also significantly overexpressed in high-grade invasive breast tumors [45].

lncRNAs also play a role in post-transcriptional gene regulation and control of cellular growth [46]. The lncRNA growth arrest-specific 5 (GAS5), which also encodes some snoRNAs, functions by sensitizing to apoptosis, a function that has been illustrated in prostate cancer cell lines [47]. The functional impact of GAS5 has also been explored in breast cancer, in which GAS5 is relatively underexpressed and, as such, maintains tumor growth potential [48].

Table 1. MicroRNAs in thyroid malignancies

miRNA	Expression	Cancer association	Associated genes	Reference
miR-221, -222, -181b, -220, -213	Upregulated	PTCs compared with normal thyroid tissue	<i>c-KIT</i>	[83]
miR-21, -31, -221, -222	Upregulated	PTCs compared with MNGs		[84]
miR-146b	Upregulated	Consistently upregulated in classical PTC	<i>NF-κB, IRAK1, TRAF6</i>	[85]
miR-165b-5p	Upregulated	PTCs; PCCL3 cell line	<i>SMAD4</i>	[86]
miR-146b, -221, -222	Upregulated	PTCs compared with normal thyroid tissue		[87–89]
miR-187, -221, -222, -146b, -155, -122a, -31, -205, -224	Upregulated	PTCs		[57]
miR-187, -224, -155, -222, -221, -146b	Upregulated	FTCs (conventional type)		[57]
miR-187, -221, -339, -183, -222, -197	Upregulated	FTCs (oncocytic type)		[57]
miR-302c, -205, -137, -187, -214, -155, -224, -222, -221	Upregulated	ATCs		[57]
miR-192, -197, -328, -346	Upregulated	FTCs (oncocytic type)		[90]
miR-30d, -125b, -26a, -30a	Downregulated	ATCs		[91]
miR-21, -146b, -221, -222	Upregulated	ATCs		[92]
miR-26a, -138, -219, -345	Downregulated	ATCs		[92]
miR-17-5p, -17-3p, -18a, -19a, -19b, -20a, -92, -106a, -106b	Upregulated	ATCs		[93]
miR-30, -200	Downregulated	ATCs compared with PTCs and FTCs	<i>TGF-β, SMAD2</i>	[94]
Let-7a	Downregulated	FTCs compared with adenomas and normal thyroid tissue	<i>FXYD5</i>	[95]
miR-191	Downregulated	FTCs, follicular adenomas and follicular variant of PTC compared with ATCs and normal thyroid tissue	<i>CDK6</i>	[96]
miR-146b, -221, -222, -155, -31	Upregulated	Aggressive compared with nonaggressive PTC	Increased <i>MET</i> expression; miR-146b increased <i>MET</i> expression in <i>BRAF</i> -positive tumors	[97]
miR-1, -34b, -130b, -138	Downregulated	Aggressive compared with nonaggressive PTC	<i>MET</i> identified as potential target gene for miR-34b and miR-1	[97]
miR-222, -146b	Upregulated	In plasma of patients with recurrent PTC		[83]
miR-375, -10a	Upregulated	MTCs	<i>YAP1</i>	[98]
miR-445	Downregulated			[98]
miR-125a-5p, -143, -23b, -425, -623, -654-3p	Upregulated	FTCs		[99]
miR-1225-3p, -1238, -135a, -150, -494, -663, -801, -923	Downregulated			[99]
miR-21, -203	Upregulated	<i>BRAF</i> -positive PTC tissues compared with <i>BRAF</i> -negative PTCs		[100]
miR-146b, -221, -222, -135b	Upregulated	PTCs with high levels of extrathyroidal invasion compared with PTCs with no extrathyroidal invasion		[101]
miR-146b	Upregulated	Overexpression increased cell migration, cell invasiveness and resistance to chemotherapy-induced apoptosis in PTCs		[102]
miR-146b-5p	Upregulated	PTC specimens of stage I, II and III and paired normal tissue	34 target genes predicted	[103]
miR-335	Downregulated		36 target genes predicted	[103]

(continued)

Table 1. (continued)

miRNA	Expression	Cancer association	Associated genes	Reference
miR-2861, -451	Upregulated	PTCs with lymph node metastasis compared with PTCs without lymph node metastasis		[104]
miR-224	Upregulated	Absence of node metastases and lower stages at diagnosis in both sporadic and familial MTCs		[61]
miR-25, -30d	Downregulated	ATCs	<i>EZH2</i>	[105]

Abbreviations: ATC, anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; miRNA, microRNA; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma.

The significant role that ncRNAs play in oncology, although still evolving, is a considerable topic. In order to enhance the clarity of this review, endocrine malignancies will be the theme of specific interest. This includes cancers of traditional endocrine origin such as thyroid carcinoma, parathyroid carcinoma, adrenocortical carcinoma, pheochromocytoma, and gastrointestinal neuroendocrine tumors. Reviews of ncRNAs as they relate to other endocrine organs, including breast [34], ovary [49], and prostate [22], can be found elsewhere.

NONCODING RNAs IN ENDOCRINE MALIGNANCIES

Surgery is the curative treatment of choice for endocrine malignancies and may also be a vital therapeutic modality for locoregional disease control and an effective palliative option. Beyond surgery, endocrine cancers have generally suffered from a lack of tailored chemotherapeutic, hormonal, or biologic therapy options. This is typified by, for instance, medullary thyroid cancer, a disease in which outcomes have not improved for more than 30 years [50, 51]. This is particularly the case in sporadic forms of the disease, and although tyrosine kinase inhibitors have been a revolution for many neuroendocrine diseases, they have failed, as of yet, to demonstrate a survival advantage for medullary thyroid cancer patients. Newer therapies are required, and our ever-expanding knowledge base regarding ncRNAs may represent an opportunity to improve treatment outcomes.

Noncoding RNAs and Thyroid Cancer

Thyroid cancer is the most common endocrine malignancy [52] and the fifth most common cancer in women [53]. The incidence of thyroid cancer has increased continuously over the last three decades [53], highlighting the need to maintain a progressive treatment paradigm. A variety of thyroid carcinoma phenotypes exist, the most common being differentiated thyroid carcinomas (DTC) that include papillary thyroid carcinoma (PTC) and follicular subtypes. The overall prognosis for DTC is excellent, with 10-year survival greater than 90% [54]. However, conventional treatment options such as surgery and radiotherapy are not effective after metastasis, after which survival declines rapidly [54]. In contrast, anaplastic thyroid carcinoma and medullary thyroid carcinoma (MTC) are rare endocrine malignancies with poorer prognosis than DTC. Anaplastic thyroid carcinoma is often rapidly fatal and has median survival of less than 6 months [54]. Although MTC maintains a 10-year survival rate greater than 70% following appropriate surgery at diagnosis, metastases are common, and efficacious therapeutic options beyond surgery are still limited [54].

Several gene mutations have been shown to be of importance in thyroid cancer, and many of them (e.g., *RET*, *RAS*)

involve the oncogenic mitogen-activated protein kinase pathway [52, 55]. Beyond this, however, epigenetic regulators (e.g., ncRNAs) are also being keenly investigated for clinical application. Although there are already established circulating biomarkers in many endocrine diseases, they are not always reliable. Circulating thyroglobulin, for example, is used as a biomarker to measure residual disease in PTC but is unreliable in 25% of cases [56]. Alternatively, novel biomarkers based on ncRNAs are on the horizon. Lee et al. [57] demonstrated that miR-222, miR-221, miR-146b, and miR-21 were lower in the serum of PTC patients after thyroidectomy (compared with controls), suggesting that elevated levels of these serum miRNAs strongly correlate with the presence of PTC. Two miRNAs in particular, miR-222 and miR-146b, also correlated with the presence of extrathyroidal extension prior to thyroidectomy. These results suggest that miRNA expression in serum not only correlates with the presence of PTC but also can predict for disease aggressiveness.

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MTC is also a disease in which differential miRNA expression has proven to be of utility. The first study investigating the miRNA profile of MTC was performed by Nikiforova et al. [58]. This involved analysis of 42 thyroid cancers and an additional 62 fine-needle aspiration (FNA) samples that were subjected to microarray studies probing for 158 different miRNAs. When compared with normal thyroid tissue, 10 miRNAs were found to be significantly upregulated, and four (miR-323, miR-370, miR-129, and miR-137) were upregulated on the order of >100-fold change. Although the paper by Nikiforova et al. provided evidence of a distinct miRNA profile for MTC, no clinical data were presented; therefore, any clinical relevance is unknown.

Following this work, the miR-200 family was implicated by Santarpia et al. in unpublished studies [59]. Microarray analysis of primary tumors (number not available) and corresponding metastatic tumor specimens yielded 16 miRNAs that were

Table 2. MicroRNAs in adrenocortical carcinomas and pheochromocytoma

miRNA	Expression	Cancer association	Associated genes	Reference
miR-541, -139-3p, -765	Upregulated	VHL pheos vs. benign sporadic pheos		[73]
miR-885-5p	Upregulated	MEN2 pheos vs. benign sporadic pheos		[73]
miR-1225-3p	Upregulated	Sporadic recurring pheos vs. benign tumors		[73]
miR-541	Downregulated	Sporadic recurring pheos vs. VHL tumors		[73]
miR-483-5p	Upregulated	Malignant pheos compared with benign pheos	<i>IGF2</i>	[76]
miR-15a, -16	Downregulated		<i>Cyclin D1</i>	[76]
miR-483-5p, -183, -101	Upregulated	Malignant pheos compared with benign pheos; can be detected in patient serum	Associated with <i>SDHB</i> gene mutation	[72]
miR-99a, -100	Downregulated	Childhood adrenocortical tumors	<i>IGF-IR; mTOR; Raptor</i>	[106]
miR-483-3p	Upregulated		<i>IGF2</i>	[106]
miR-7, -129-3p	Downregulated	ACTs compared with normal adrenal cortices		[70]
miR-335, -195	Downregulated	ACAs compared with ACCs		[70]
miR-483-5p	Upregulated		<i>IGF2</i>	[70]
miR-184, -503, -210	Upregulated	ACCs compared with ACAs		[107]
miR-214, -511	Downregulated	ACCs compared with ACAs and normal adrenal cortices		[107]
miR-375	Downregulated	ACTs compared with normal adrenal cortices		[108]
miR-483-5p	Upregulated	Upregulated in ACCs compared with ACAs and normal cortices; upregulated in ACTs compared with normal cortices	<i>IGF2</i>	[108]
miR-195, -125b, -100	Downregulated	Downregulated in ACCs compared with ACAs and normal cortices; downregulated in ACTs compared with normal cortices		[108]
miR-195, -335	Downregulated	Downregulated in tumor and serum samples of ACC patients (compared with ACA or healthy controls)		[44]
miR-483-5p	Upregulated	Upregulated in tissue ACCs compared with ACAs or healthy controls; serum miR-483-5p detected only in aggressive ACCs	<i>IGF2</i>	[44]

Abbreviations: ACA, adrenocortical adenoma; ACC, adrenocortical carcinoma; ACT, adrenocortical tumor; MEN2, multiple endocrine neoplasia type 2; miRNA, microRNA; pheos, pheochromocytomas.

found to be differentially expressed between primary and metastatic tumor tissue. Further bioinformatic analyses identified purported gene targets known to be important for cell adhesion and migration. Subsequent miR-200 transfection of two human MTC cell lines (TT and MZ-CRC-1) induced a reduction in cell adhesion and an increase in cell detachment in vitro and characteristics thought to be consistent with a tendency to metastasize and more aggressive clinical behavior [59].

More recent work has been undertaken to define the miRNA profile of MTC at the Kolling Institute of Medical Research. Following array studies, validation work confirmed that miR-375 and miR-183 were significantly overexpressed in sporadic MTC (SMTC) versus hereditary MTC (HMTc) cases of disease. MiR-183 expression was also shown to be significantly associated with high-risk *RET* mutation status in addition to a tendency toward development of residual disease, lateral lymph node metastases, and mortality [60].

The most recent miRNA studies of MTC were published in 2012 by Mian et al. [61]. These studies examined clinical specimens of 34 cases of SMTC, 6 cases of HMTc, and an additional 2 cases of C-cell hyperplasia, with the aim of correlating miRNA expression with *RET* gene mutation status and outcome. In summary, overexpression of a number of miRNAs was defined in MTC (SMTC and HMTc were grouped together) and C-cell hyperplasia specimens (miR-21, miR-127,

miR-154, miR-224, miR-323, miR-370, miR-9*, miR-183, and miR-375). More specifically, lower levels of miR-127 were observed in cases of SMTC with somatic *RET* mutations, as compared with wild-type *RET*. With regard to clinical outcome, miR-224 expression also correlated with an improved prognosis. Mian et al. concluded that miRNAs are significantly dysregulated in MTC and suggested that this may be a fundamental event in the pathogenesis of C-cell carcinogenesis [61].

The studies of Nikiforova et al. [58] also demonstrated that miRNA analysis of FNA tissue not only is possible but also improves the accuracy of this diagnostic test in assessment of the thyroid nodule. When at least one miRNA was overexpressed more than twofold, FNA test sensitivity improved to 100%, specificity was 94% and accuracy 95% [58]. With regard to potential biopsy of metastatic disease, it has also been shown that miRNA profiles in lymph node metastases are similar specifically to the primary tumor in thyroid cancer [62].

A number of lncRNAs have also been associated with thyroid carcinomas, including the lncRNAs AK023948 [63] and NAMA [64], which are both downregulated in PTC. AK023948 represents a possible candidate gene for PTC susceptibility [63], and NAMA was found to be a downstream target gene of the mitogen-activated protein kinase pathway and is associated with cell-growth arrest [64]. Papillary thyroid carcinoma susceptibility candidate 3 (PTCSC3A) is another lncRNA found

Table 3. MicroRNAs in gastrointestinal neuroendocrine malignancies

miRNA	Expression	Cancer association	Reference
miR-204	Upregulated	Insulin-secreting pNETs	[78]
miR-103, miR-107	Upregulated	Distinguishes pNET from normal pancreatic tissue	[78]
miR-155, -10b, -133a, -145, -146, -122	Downregulated	Metastatic ileal NETs	[109]
miR-183, -488, -19a, -19b	Upregulated		[109]
miR-31, -129-5p, -133a, -125	Downregulated	Metastatic small intestinal NETs	[79]
miR-96, -182, -183, -196a, -200a	Upregulated		[79]
miR-653, -7, -489, -1224-5p	Upregulated	Distinguishes colorectal NET from normal colorectal tissue	[110]
miR-21, -155	Upregulated	Higher grade NETs compared with lower grade NETs	[81]

Abbreviations: miRNA, microRNA; NET, neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor.

to be significantly underexpressed in PTC, with restoration of PTCSC3A in PTC cell lines inhibiting cell growth [65]. The significance of miRNAs in thyroid cancer is now also becoming a reality for additional lncRNAs candidate markers.

Noncoding RNAs and Parathyroid Cancer

Parathyroid carcinoma is a rare cause of primary hyperparathyroidism and may lead to intractable, potentially life-threatening hypercalcemia [54]. The rare nature of parathyroid carcinoma has meant that there are few studies examining the role that ncRNAs play in the pathogenesis of this disease. Current opportunities to exploit ncRNAs do exist, particularly with regard to diagnosis, which is frequently difficult, given the absence of definitive histological features and the requirement for local tissue invasion, by which time curative resection is not possible [54].

Aberrant parathyroid carcinoma miRNA expression has been identified in a small number of studies [66–68], suggesting that there may be a miRNA profile of diagnostic and prognostic potential. Corbetta et al. [66], for example, have shown that when compared with normal glands, malignant parathyroid tissue overexpresses miR-222 and miR-503. In addition, miR-296 and miR-139 were reportedly underexpressed in malignant tissue. Interestingly, miR-139 is located at a fragile chromosomal region often lost in multiple endocrine neoplasia type 1, implying that this miRNA may harbor significance in multigland endocrinopathy [66]. Many overexpressed miRNAs in parathyroid carcinoma are located at the *C19MC* genomic cluster. The loss of promoter methylation at the *C19MC* cluster is associated with high calcium levels and metastatic disease, suggesting an oncogenic role for these overexpressed miRNAs [68].

The functional role of what appears to be newly identified differential expression is beginning to be unveiled. Although current ncRNA research into parathyroid carcinoma is presently limited, it is a disease that would appear to be ideally suited to this realm of scientific exploration. The need for improved diagnostic criteria in particular should be an adequate stimulus for ongoing research interest.

Noncoding RNA in Adrenocortical Carcinoma and Pheochromocytoma

Adrenocortical carcinoma (ACC) is an aggressive tumor of the adrenal gland, associated with frequent metastasis and poor survival [69]. Patients with ACC have suffered from diagnostic criteria that, arguably, are still lacking [70], leading to delays in diagnosis and difficulty committing to appropriate therapy. Present treatment regimens are poorly tolerated, and tailored

therapy has yet to become a reality. Clearly, ncRNAs may fill a significant biomarker, diagnostic, and therapeutic void for this disease. Soon et al. investigated whether differential miRNA expression could identify potential prognostic markers and therapeutic targets in ACC using a microarray analysis [71]. MiR-483-5p was found to be overexpressed in ACC compared with both adenoma and normal tissue. Cancers also demonstrated underexpression of miR-335 and miR-195. Clinical data correlation also yielded biomarker potential, with ACC underexpression of miR-195 and overexpression of miR-483-5p predicting poorer disease-specific prognosis.

These results have been further validated more recently by Chabre et al., who confirmed miR-483-5p overexpression and miR-195 underexpression in ACC. In addition, differential expression of these miRNAs also correlated with a more aggressive phenotype of disease, associated with larger tumor size and poorer prognosis [44]. Significantly, the authors were also able to quantify the miRNA expression in patient serum, and levels of both miR-195 and miR-483-5p were shown to decrease significantly following resection of the primary ACC. This suggested that serum miRNA expression may be associated with a specific tumor burden, which has implications for the use of circulating miRNAs as biomarkers of disease.

In contrast to the previous two studies, the works of Ozata et al. [69] failed to demonstrate a significant association between miR-483-5p or miR-195 and clinical outcome in their ACC cohort. This may be indicative of a heterogeneous patient population and may also relate to the current reliability of ncRNA technology that is not presently commercially available on a large scale. More work is required to ensure that ncRNA results fulfill the requirements of a clinically useful test, namely, to be valid, reliable, and reproducible. Table 3 summarizes the ncRNA research to date in ACCs and pheochromocytomas.

Pheochromocytomas are rare, catecholamine-producing endocrine tumors of chromaffin cell origin that originate in the adrenal medulla [54, 72, 73]. They can also occur in extra-adrenal sites such as the chest and the pelvis [74]. They are unique tumors because they often occur within the context of hereditary endocrine syndromes and genetic mutations, such as multiple endocrine neoplasia type 2 and von Hippel-Lindau syndrome. Currently, there are no reliable histomorphological features to distinguish between benign and malignant pheochromocytoma [72], and a definitive diagnosis of malignancy relies on tumor metastases at sites where chromaffin tissue is normally absent [74, 75]. As in the previously discussed diagnostic conundrums of parathyroid carcinoma and ACC,

ncRNAs may represent an alternative diagnostic tool with which to clarify a specific diagnosis and may have far-reaching clinical consequences.

Currently, there are no reliable histomorphological features to distinguish between benign and malignant pheochromocytoma, and a definitive diagnosis of malignancy relies on tumor metastases at sites where chromaffin tissue is normally absent. As in the previously discussed diagnostic conundrums of parathyroid carcinoma and ACC, ncRNAs may represent an alternative diagnostic tool with which to clarify a specific diagnosis and may have far-reaching clinical consequences.

Meyer-Rochow et al. were among the first groups to explore miRNA expression in malignant pheochromocytoma by using a microarray expression analysis [76]. Overexpression of miR-483-5p was identified in malignant tumors (compared with benign and normal adrenal tissue), and this was also shown to positively correlate with *IGF2* overexpression. In addition, miR-15a and miR-16 were found to be underexpressed. The functional roles of miR-15a and miR-16 were further investigated in vitro, and it was determined they induced cell cycle arrest and reduced cellular proliferation [76]. From a translational viewpoint, the authors also examined the clinical utility of differential miRNA expression and reported that high *IGF2* mRNA and low miR-15a expression could distinguish malignant from benign tumors with 80% sensitivity and 100% specificity [76]. These findings articulate how existing diagnostic schemas may benefit from the addition of ncRNA expression profiles.

These results have been supported by the confirmatory studies of Patterson et al., who also identified overexpression of miR-483-5p in malignant pheochromocytomas [72], in addition to underexpression of miR-183 and miR-101. Such differential miRNA expression was also validated in serum samples. Beyond these findings, Tombol et al. [73] demonstrated that elevated expression of miR-885-5p and miR-1225-3p is seen in multiple endocrine neoplasia type 2-related and sporadic, recurring pheochromocytomas, respectively [73].

Current genetic markers for endocrine malignancies such as pheochromocytoma are of great utility but are not infallible. As discussed, ncRNA research may represent an opportunity to improve diagnostic and prognostic accuracy by identifying subtle epigenetic differences between tumors. This may also reveal the possibility of tailored therapy for diseases like endocrine malignancies that largely fail to respond to conventional chemotherapeutic regimens.

Noncoding RNAs and Neuroendocrine Tumors

There are few studies in the literature relating to ncRNAs and (non-MTC) neuroendocrine malignancies. Neuroendocrine

tumors (NETs) most often occur in the intestines, pancreas, and lung and can be classified as functional NETs (hormone secreting) or nonfunctional (non-hormone secreting) [77]. Pancreatic endocrine tumors (PETs) are rare cancers that account for ~1%–2% of all pancreatic malignancies, and 90% of them occur sporadically [77]. The only study in the literature to our knowledge investigating ncRNAs and PETs [78] found differential microRNA expression between PETs and normal pancreatic tissue, as well as being able to distinguish between pancreatic tumors of an islet cell origin from those of an acinar cell origin. Overexpression of miR-21 was also highly correlated with the presence of liver metastasis [78].

Two studies have investigated ncRNAs and small intestinal NETs, and only one study exists presently with a focus on lung NETs. miRNA-196a was shown to be overexpressed in small intestinal NETs in both studies [79, 80]. Overexpression was validated in malignant samples, and expression was differential between locally advanced and metastatic NET cell lines. Such differential expression presumably occurred through the proliferative effect of miR-196a on the *PI3K/AKT/mTOR* pathway and synthesis of *HOXB/C* genes [80].

Similarly, Lee et al. found miR-21 and miR-155 to be overexpressed in high-grade, invasive pulmonary NETs compared with carcinoid pulmonary NETs [81]. The oncogenic effect of miR-155 in these NETs was proposed to be due to the miR-155 effect on *transforming growth factor-β* to induce cell migration, invasion, and epithelial-mesenchymal transition [81].

Although basic scientific exploration of the role that ncRNAs play in NETs continues, there is little data available that is of translational significance. As with the other endocrine malignancies discussed, NETs are a disease that requires a dedicated research effort to forge new management paradigms, possibly based on ncRNA discovery [82].

CONCLUSION

This review highlights the burgeoning potential of noncoding RNA as a diagnostic, prognostic, and therapeutic tool in cancer research. There is no question that both small and long ncRNAs have vital biological roles that influence a myriad of different pathways that are implicated in the oncogenesis and metastasis of cancer. Present preclinical evidence in relation to endocrine malignancy has great potential to transform future management of a unique group of diseases that have failed to respond to conventional management. Epigenetic ncRNA regulation is of great importance and should be harnessed in the future as a means of not only enhancing our understanding of endocrine malignancy but also, ultimately, of translating current knowledge into therapeutic success.

AUTHOR CONTRIBUTIONS

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DISCLOSURES

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