OncoTargets and Therapy

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REVIEW

The Current State of Research Regarding the Role of Non-Coding RNAs in Cutaneous Squamous Cell Carcinoma

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Abstract: Skin cancers, including those of both both melanoma and non-melanoma subtypes, remain among the most common forms of human cancer. Non-melanoma skin cancers are typically further differentiated into the basal cell carcinoma and cutaneous squamous cell carcinoma (cSCC) categories. Current approaches to diagnosing and treating cSCC remain unsatisfactory, and the prognosis for patients with this disease is relatively poor. Recent advances in high-throughput sequencing have led to an increasingly robust understanding of the diversity of non-coding RNAs (ncRNAs) expressed in both physiological and pathological contexts. These ncRNAs include microRNAs, long ncRNAs, and circular RNAs, all of which have been found to play key functional roles and/or to have value as diagnostic biomarkers or therapeutic targets in a range of different disease contexts. The number of ncRNAs associated with cSCC continues to rise, and as such, there is clear value in comprehensively reviewing the functional roles of these molecules in this form of cancer in order to highlight future avenues for research and clinical development.

Keywords: cSCC, no-coding RNA, miRNA, lncRNA, circRNA

Introduction

Skin cancer is a highly prevalent disease in humans and is typically classified into melanoma and non-melanoma categories, with the latter category including the basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) skin cancer subtypes.[1] cSCC remains the second most common skin cancer subtype, accounting for 20% of all skin cancer deaths globally, with 200,000 newly diagnosed cases annually in the United States alone.[2–4] Recent advances in surgical, radiotherapeutic, and chemotherapeutic interventions have led to some improvements in cSCC patient prognosis, but at present, the prognosis for patients with this disease remains relatively poor. As such, it is vital that further studies continue to explore the mechanistic basis for cSCC in order to identify novel diagnostic, prognostic, and therapeutic targets that can guide patient treatment and improve survival outcomes.

Advances in next-generation sequencing (NGS) technologies in recent decades have led to the identification of countless distinct non-coding RNA transcripts within cells, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). The best understood of these molecules are miRNAs, which are short RNAs (~22 nt) capable of directly binding to complementary segments in the 3′-untranslated region (UTR) of target mRNA molecules in order to regulate gene

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http://doi.org/10.2147/OTT.S271346

expression.[5–7] Studies of miRNAs thus typically focus on identifying the target genes governed by these non-coding RNA molecules. In contrast, lncRNAs are significantly longer (>200 nt) and were previously regarded as non-functional or "junk" RNA molecules.[8,9] However, more recent studies have found that lncRNAs are important in both physiological and pathological contexts, wherein they can play diverse roles including modulating mRNA splicing, regulating chromatin remodeling, sequestering miRNAs, or binding to and altering the subcellular localization of specific proteins.[8–11] cirRNAs were first detected in studies of viral particles,[12] with further research revealing them to be produced by the back-splicing of mono-exonic, multi-exonic, or intronic gene regions. Because they lack a poly-A tail, these RNA molecules are better able to resist exonuclease-mediated degradation than are their linear counterparts.[13] Although not as well understood as miRNAs and lncRNAs, circRNAs are also thought to play important roles in diseases, wherein they can act as competing endogenous RNA (ceRNA) sponges capable of sequestering specific RNAs,[14,15] interact with RNA binding proteins,[16,17] and modulate coding peptides.[18,19] Countless studies have examined the roles of particular non-coding RNA molecules in specific cancers, revealing them to have value as diagnostic or prognostic biomarkers and to represent potentially viable therapeutic targets.[20–22] In the present review, we specifically discuss recent studies regarding the role of non-coding RNA molecules in cSCC, we discuss the latest research advance of non-coding RNAs involved in cSCC, with the goal of highlighting key clinically relevant targets that may help to guide patient diagnosis and treatment. In addition, most of these non-coding RNAs may be of value for the diagnosis and treatment of cSCC.

miRNAs in cSCC

miR-21

The overexpression of miR-21 has been found to be a hallmark of several different tumor types, including cSCC, wherein it has been shown to drive the enhanced invasion and metastasis of these tumor cells引用文献PMID: 32,360,623, 31,371,997. Well-characterized targets of miR-21 with known relevance to cancer development and progression include phosphatase tensin homolog (PTEN) and programmed cell death 4 (PDCD4), with miR-21 leading to the downregulation of both of these tumor suppressor genes. Indeed, in a study of A431 cells, Li et al found that silencing miR-21 ultimately led to the enhanced expression of both PDCD4 and PTEN in these cells.[23] Consistent with these observations, Charbel et al found that miR-21 was able to suppress the activity of the GRHL3-PTEN axis, which in turn bolstered PI3K/Akt/mTOR signaling in these cells and thereby drove cSCC development and progression.[24] These previous findings thus highlight the potential for miR-21 to serve as a viable therapeutic target for the treatment of cSCC.

miR-365

Several studies have identified an oncogenic role for miR-365.[25–27] Ding et al found that the UVB irradiation of murine NIH3T3 cells was sufficient to induce the upregulation of this miRNA, suggesting that its expression may be closely linked to UV radiation exposure. They further demonstrated that miR-365 was capable of promoting oncogenesis in vitro and in vivo at least in part via targeting nuclear factor I/B (NFIB), which is a tumor suppressor gene that can promote the cell cycle arrest and apoptotic death of malignant cSCC cells.[28,29] As such, this miR-365/NFIB axis may be amenable to therapeutic intervention in cSCC patients.

miR-31

Unlike the two miRNAs discussed above, miR-31 has been shown to play distinct roles in different subtypes of cancer. In breast cancer, for example, reduced miR-31 expression levels are associated with higher rates of metastasis, whereas studies of colorectal cancer suggest that miR-31 overexpression is linked to enhanced invasion and more advanced TNM stage.[30,31] Work by Wang et al indicated that miR-31 expression levels were increased in cSCC, wherein this miRNA was able to enhance tumor cell proliferation and migration, highlighting it as a potentially viable therapeutic target in this cancer type.[32] The variable expression levels and inconsistent molecular functions of miR-31 in different cancers indicate that it is associated with more pronounced tissue specificity and may exhibit promising biomarker capacity.

miR-34a

Lefort et al were the first to highlight a potential role for miR-34a in cSCC, as they found that the expression of this miRNA rose during the process of keratinocyte differentiation, whereas its expression was reduced in SCC cell lines and primary tumor samples, as well as in abnormally differentiating primary human keratinocytes (HKCs). These researchers further identified SIRT6 as a miR-34a target gene in HKCs, with the knockdown of SIRT6 expression being sufficient to enhance cellular proliferation, yielding a phenotype comparable to that observed

upon miR-34a upregulation.[33] These findings further highlight this miR-34a/SIRT6 axis as another potential driver of cSCC development that may amenable to therapeutic targeting.

miR-125b

Xu et al first reported the downregulation of miR-125b in cSCC tissue samples, and they further demonstrated that in these cSCC cells this miRNA was capable of suppressing tumor cell proliferation, migration, and invasion.[34] They identified matrix metallopeptidase 13 (MMP13) as a miR-125b target gene, with reduced miR-125b expression in cSCC thus leading to increased MMP13 expression. These results, therefore, indicate that miR-125b functions as a tumor suppressor miRNA in cSCC, and may thus be of value as a diagnostic or prognostic biomarker in patients with this disease.

miR-199a

A number of different tumor types have been found to exhibit miR-199a dysregulation.[35,36] Research by Wang et al suggested that the expression of this miRNA was markedly reduced in cSCC and that it was negatively correlated with CD44 expression.[37] As CD44 encodes a cell surface glycoprotein that is involved in adhesion, migration, and metastasis, this work thus suggested that miR-199a directly regulates CD44 expression and thus represents a viable means of targeting CD44 in the context of cSCC.

lncRNAs in cSCC

Hotair

HOTAIR (HOX transcript antisense intergenic RNA) is a lncRNA that is encoded in the 12q13.13 region of the human genome and that is closely linked to the onset of cervical and breast cancers, wherein it can promote tumor cell migration and proliferation.[38,39] Work by Sand et al has further demonstrated that HOTAIR upregulation is evident in cSCC, with these results being confirmed both via lncRNA microarray and qRT-PCR.[40] More recently, Yu et al confirmed that cSCC cell lines exhibit HOTAIR upregulation, which in turn enhances their migratory and proliferative activity and bolsters their ability to undergo the epithelial-mesenchymal transition (EMT).[41] HOTAIR is believed to function as a ceRNA capable of sequestering miRNAs including miR-326, which leads to the increased expression of the miR-326 target gene PRAF2 and results in enhanced cell migration and proliferation. This HOTAIR/miR-326/PRAF2 axis therefore offers key insights into the mechanistic basis for cSCC.

TINCR

The use of photodynamic therapy (PDT) as a minimally-invasive treatment for premalignant and malignant skin lesions has been increasingly explored in recent years, as this technique does not induce scar formation. SCCs have successfully been treated via ALA (5-aminolevulinic acid)-PDT, with such treatment inducing autophagy and the apoptotic death of malignant cells. The 3.7 kb lncRNA known as terminal differentiation-induced ncRNA (TINCR) has been shown to mediate the post-transcriptional regulation of human epidermal cellular differentiation.[42] Research by Zhou et al suggests that ALA-PDT can promote enhanced expression of TINCR via an ERK1/2-SP3 pathway, whereupon it was capable of inducing apoptosis and autophagy in A431 cells.[43] This thus suggests that TINCR represents a viable lncRNA target for the therapeutic treatment of cSCC.

LINC01048

Chen et al identified the lncRNA LINC01048 as being significantly upregulated in recurrent cSCC tissue samples relative to non-recurrent cSCC or paracancerous normal tissues.[44] They further found that LINC01048 expression was negatively correlated with overall survival and cure rates in cSCC patients. At a mechanistic level, they found that knocking down LINC01048 was sufficient to impair cSCC cell growth in vitro and in vivo. Specifically, they determined that LINC01048 upregulation was driven by USF1, and once upregulated, LINC01048 was able to bind to TAF15 in order to drive enhanced YAP1 expression. This study thus highlights the potential relevance of LINC01408 in the context of cSCC, making it yet another potentially valuable diagnostic and or therapeutic target in individuals with this disease.

LINC00520

Mei et al established LINC00520 as a tumor suppressor lncRNA that is downregulated in cSCC, and that impairs cSCC cell growth and metastasis in vitro and in vivo.[45] They further found that LINC00520 functioned at least in part by targeting and inhibiting EGFR (epidermal growth factor receptor) expression and thereby disrupting the downstream PI3K/Akt signaling that is essential to robust tumor cell growth. Together, these results thus highlight LINC00520 as another promising biomarker of cSCC.

PICSAR

The overexpression of LINC00162 in cSCC cell lines was originally reported by Piipponen et al, who detected this dysregulation through whole transcriptome analysis. They then designated this lncRNA as p38 inhibited cSCC-associated lncRNA (PICSAR).[46] When these researchers knocked down PICSAR, they found that this significantly impaired cSCC cell growth and migration in vivo and in vitro. They further determined that this lncRNA functions at least in part via inhibiting the MAPK phosphatase DUSP6, thereby leading to enhanced ERK1/2 pathway activation and more robust tumor cell growth. PICSAR thus represents another ncRNA with the potential to serve as a diagnostic biomarker or therapeutic target in cSCC.[47]

AK144841

Ponzio et al first detected the upregulation of the lncRNA AK144841 in cSCC cells.[48] While AK144841 expression was largely absent in normal murine skin, it was markedly upregulated in murine cSCC cells. They further found that AK144841 was able to inhibit the expression of several different tumor suppressor genes, including members of the late cornified envelope-1 (Lce1) family, as well as *Cgref1, Brsk1, Basp1, Dusp5*, and *Btg2*, with AK144841 expression being negatively correlated with that of these genes. These researchers additionally determined that a human isoform of AK144841 was similarly upregulated in cSCC tissue samples, suggesting that detecting hAK144841 expression in precancerous lesions may allow for the more efficient detection of potentially malignant tumors, thereby guiding clinical treatment strategies.

circRNAs in cSCC

hsa_circ_0070934

At present, relatively limited research has been conducted exploring the functional relevance of circRNAs in cSCC. Work by Sand et al conducted in 2015 sought to characterize circRNA expression profiles in cSCC and normal

Table 1 Overview of the ncRNAs Have Been Reported in Cutaneous Squamous Cell Carcinoma

ncRNA	Related Targets	Function	Regulation	Refs
miR-21	PTEN, PDCD4	Oncogenic	Up-regulation	[23,24]
miR-365	NIFB	Oncogenic	Up-regulation	[28,29]
miR-31	ITGA5, RDX WAVE3	Oncogenic	Up-regulation	[32]
miR-34a	SIRT6	Tumor suppressor	Down-regulation	[33]
miR-125b	MMP13	Tumor suppressor	Down-regulation	[34]
miR-199a	CD44	Tumor suppressor	Down-regulation	[37]
HOTAIR	miR-326/PRAF2	Oncogenic	Up-regulation	[40,41]
TINCR	ERK1/2-SP3 pathway	promote ALA-PDT-induced apoptosis and autophagy	Down-regulation	[43]
LINC01048	TAF15/YAP1	Oncogenic	Up-regulation	[44]
LINC00520	EGFR	Tumor suppressor	Down-regulation	[45]
PICSAR	DUSP6	Oncogenic	Up-regulation	[46]
AK144841	Lce1, Cgref, Brsk1, Basp1, Dusp5, Btg2	Oncogenic	Up-regulation	[48]
hsa_circ_0070934	miR-1238/miR-1247-5p	Oncogenic	Up-regulation	[50]
hsa_circ_001937	miR-597-3p/FOSL2	Oncogenic	Up-regulation	[51]
circPVT1	NA	Oncogenic	Up-regulation	[52]

paracancerous tissue samples, leading to the identification of 143 and 179 circRNAs that were significantly up- and down-regulated in cSCC tissues, respectively (fold-change≥2 and p <0.05).[49] The authors further employed an Arraystar miRNA target prediction software in order to identify the miRNA targets of these circRNAs. While this study highlighted the differential expression of circRNAs in cSCC, the authors did not conduct further functional studies of the role of these molecules in this disease context.

In an effort to expand on these above results, An et al identified hsa_circ_0070934 from among the circRNAs that were upregulated in cSCC in the above study and analyzed the functional relevance of this circRNA in depth.[50] They were able to confirm that hsa_circ_0070934 expression was elevated in both cSCC tissues and cells via qRT-PCR. From a functional perspective, they further found that elevated expression of hsa_circ_0070934 led to markedly enhanced cSCC cell proliferation, migration, and invasion. Using dual-luciferase reporter constructs, they were also able to confirm that hsa_circ_0070934 was able to directly interact with miR-1238 and miR-1247-5p, although they did not identify the relevant targets of these miRNAs nor did they rule out the possibility that this circRNA plays additional functional roles in cSCC. These results thus highlight the potential functional relevance of circRNAs in cSCC, although more research will be needed to understand the magnitude of their relevance in this disease context.

hsa_circ_001937

hsa_circ_001937 was identified as a 2850 nucleotide exonic circRNA that is encoded on chromosome 16引用PMID: 30,259,364. Gao et al identified differentially expressed circRNAs in cSCC using the Arraystar Human circRNA chip引用PMID: 33,000,177, leading to the discovery that

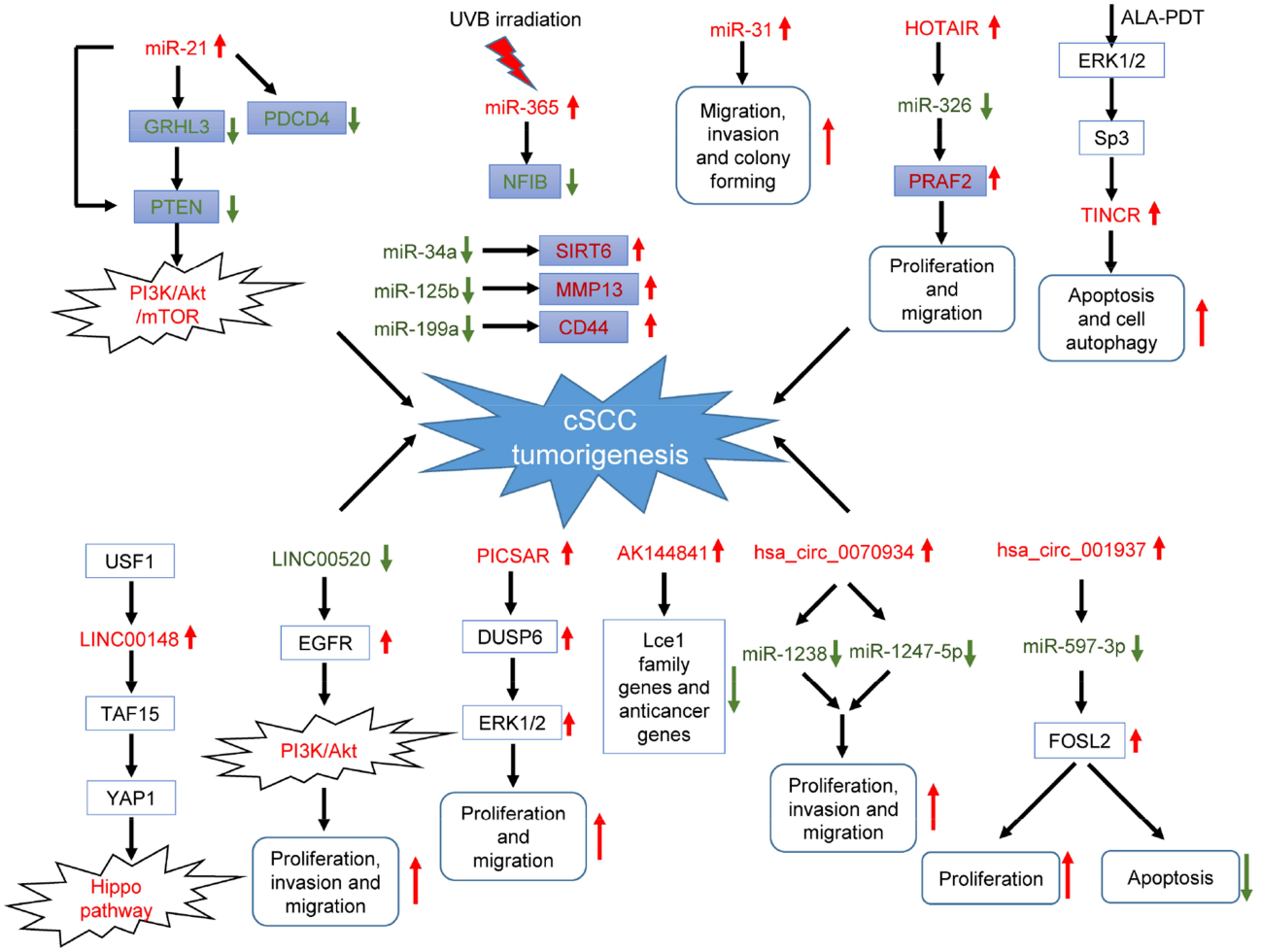

Figure 1 The biological roles of non-coding RNAs in cSCC.

hsa_circ_001937 expression was upregulated by more than 14-fold in cSCC tissues. From a mechanistic perspective, the authors determined that hsa_circ_001937 was able to act as ceRNA to sequester miR-597-3p, thereby modulating FOSL2 expression in these cells. As such, the hsa_circ_001937/miR-597-3p/FOSL2 axis influences cSCC progression and represents a potential therapeutic target for cSCC patients.

circPVT1

The 410 nucleotide-long circPVT1 originates from exon 2 of the *PVT1* gene. In our previous study, we conducted circRNA sequencing using 3 pairs of cSCC tissues in order to profile cSCC-specific circRNAs引用PMID: 32,764,965. A total of 449 dysregulated circRNAs were identified through this analysis, and we found that circPVT1 was upregulated 5-fold in cSCC tissues. We further confirmed the upregulation of this circRNA in relevant tumor cell lines and in 30 pairs of tumor and paracancerous tissues via qRT-PCR. Notably, circPVT1 has been shown to be overexpressed and to function as an oncogene in multiple cancers 引用PMID: 30,590,312, 27,986,464, indicating that it may similarly play an oncogenic role in cSCC. In vitro assays revealed that silencing circPVT1 inhibited the migration and invasion of cSCC cells. A ceRNA network was additionally constructed to explore circRNA-miRNA-mRNA interactions, leading to the conclusion that circPVT1 was significantly involved in this regulatory network. These findings indicated that circPVT1 was also able to promote cSCC progression via sequestering target miRNAs and thereby influencing the expression of specific mRNAs. However, further in vitro/in vivo assays are requires to confirm the mechanistic basis for these observations, and these assays represent the focus of our ongoing work.

Concluding Remarks

In this review, we have provided a comprehensive overview of non-coding RNAs that have been found to be related to the development and/or progression of cSCC (Table 1 and Figure 1). While the mechanisms whereby miRNAs function are fairly well understood, the functionality of lncRNAs and circRNAs in the context of oncogenesis remains to be fully explored. As highlighted in the present article, these non-coding RNAs have the potential to serve as diagnostic and/or therapeutic biomarkers in cSCC, and they additionally offer broad mechanistic insights into transcriptomic functionality in human cells. As NGS technologies continue to advance, additional ncRNAs will likely be identified and better characterized. Further studies focused on the role of circRNAs in cSCC will be invaluable, as these ncRNAs are poorly studied in this disease context. In addition, some reports suggest that in certain contexts, ncRNAs can be translated into functional proteins or polypeptides,[51–56] thus highlighting another potential mechanism whereby these molecules can modulate oncogenesis. Further research regarding these mechanisms will prove essential to advancing present understanding of cSCC development and treatment.

Acknowledgments

This work was supported by a grant from: the Science & Technology Fund of Liaoning Province (grant no. 201501013); the Distinguished Professor Foundation of Liaoning Province (grant no. Liao (2012)145).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no potential conflicts of interest.

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