



## Non-coding RNAs in skin cancers: An update

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### ARTICLE INFO

#### Article history:

Received 21 November 2016

Received in revised form

23 November 2016

Accepted 23 November 2016

Available online xxx

#### Keywords:

Skin cancer

Non-coding RNA's

miRNA

Cell proliferation

Invasion

Metastasis

### ABSTRACT

Skin cancers are the most common form of cancer in humans. They can largely be categorized into Melanoma and Non-melanoma skin cancers. The latter mainly includes Squamous Cell Carcinoma (SCC) and Basal Cell Carcinoma (BCC), and have a higher incidence than melanomas. There has been a recent emergence of interest in the role of non-coding RNA's in pathogenesis of skin cancers. The transcripts which lack any protein coding capacity are called non-coding RNA. These non-coding RNA are further classified based on their length; small non-coding RNA (<200 nucleotides) and long non-coding RNA (>200 nucleotides). ncRNA They are involved at multiple transcriptional, post transcriptional and epigenetic levels, modulating cell proliferation, angiogenesis, senescence and apoptosis. Their expression pattern has also been linked to metastases, drug resistance and long term prognosis. They have both diagnostic and prognostic significance for skin cancers, and can also be a target for future therapies for cutaneous malignancies. More research is needed to further utilize their potential as therapeutic targets. © 2016 The Authors. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

### 1. Introduction

Skin cancers are the most common form of cancer in humans. They can largely be categorized into Melanoma and Non-melanoma skin cancers. The latter mainly includes Squamous Cell Carcinoma (SCC) and Basal Cell Carcinoma (BCC), and have a higher incidence than melanomas [1]. There has been a recent emergence of interest in the role of non-codingRNA's (ncRNAs) in pathogenesis of skin cancers. Majority of the studies focus on the role of ncRNA in epigenetics of melanoma and there is only limited amount of information available on non-melanoma skin cancers. Herein, we attempt to review the role of non-coding RNA in pathogenesis as well as potential therapeutic targets for skin cancers.

Recent advances in sequencing technologies have questioned the possible roles of entities that were previously considered to have minimal or insignificant contribution in disease pathogenesis and epigenetics. Although >75% of human genome is selectively transcribed, only a small portion (1–2%) of transcripts are eventually translated into proteins. The transcripts which lack any protein coding capacity are called non-coding RNA. These non-coding RNA are further classified based on their length; small

non-coding RNA(<200 nucleotides) and long non-coding RNA (>200 nucleotides). Small non-codingRNA largely consists of microRNA (<20 nucleotides) and small nucleolar RNA. MicroRNAs are the most extensively studied group of RNAs which function in negative regulation of gene expression by binding to target mRNA leading to induction of degradation or inhibition of its translation. Long non-coding RNAs also possess functional capacity owing to their longer lengths and additional ability to fold upon themselves forming tertiary structures [2,3].

The growing body of evidence suggests that ncRNA regulate key tumor pathways and have shown to be involved in almost all human tumors. They are involved at multiple transcriptional, post transcriptional and epigenetic levels, modulating cell proliferation, angiogenesis, senescence and apoptosis (See Fig. 1). Their expression pattern has also been linked to metastases, drug resistance and long term prognosis [4–9]. Resistance of cancers to chemotherapeutic agents is the main clinical barrier to cure and improve treatment outcomes. Therefore, better understanding of the role of non-coding RNA will help us improve treatment and prognosis of skin cancers.

### 2. Role of ncRNA in skin cancers

Skin cancers are becoming a leading cause of morbidity and mortality worldwide. Non-melanoma skin cancers are more

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<http://dx.doi.org/10.1016/j.ncrna.2016.11.003>

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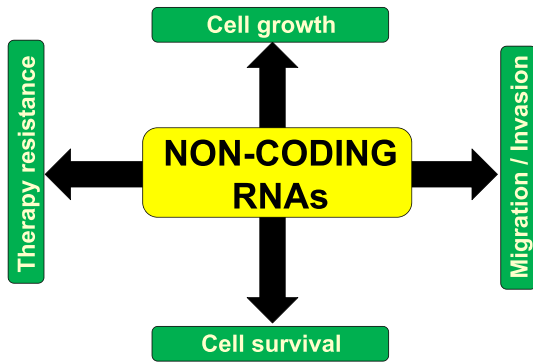


Fig. 1. Role of ncRNAs in cancers.

common than melanomas but the latter is a major cause of skin cancer related deaths. Early detection of melanoma is very important in improving survival rates. Treatment options for advanced melanoma are limited and needs more innovative strategies and targets. Pathogenesis of melanoma is very complex and involves interaction between a network of genes, regulatory mechanisms and various signaling pathways. Non-codingRNAs have garnered huge interest in the recent years regarding their role in tumorigenesis, not limited to melanomas. Their potential role in pathogenesis and as an early prognostic indicator needs further elucidation.

Melanocytes are pigment producing cells that are derived from neural crest cells. A series of steps ultimately lead to melanoblast formation and transport as melanosomes to keratinocytes. A number of melanocyte-specific proteins are expressed on melanocytes such as: Tyrosinase, Tyrosinase Protein 1 and 2, Melanosomal Matrix Protein and Microphthalmia Transcription Factor (MITF) [10]. Other genes including MITF, SOX 10, PAX3, [11–13] members of the Wnt and notch pathways [14–16], KIT and cyclins [17] all play important roles in stepwise metamorphosis of melanocytes. In addition to the contribution of protein coding genes, many non-coding genes also have a vital contribution to the signaling process. Small and long non-codingRNAs are discussed in detail pertaining to their role in melanocyte biology and cancer formation. Most commonly implicated miRNAs in skin cancers have been described in Table 1.

### 2.1. MicroRNAs (miRNA) in melanocyte biology and immune response

miRNAs are small noncoding RNA (<200 nucleotides) that are involved in fine tuning of more than 60% of proteins [18,19]. Several

studies have confirmed the aberrant expression of miRNAs in melanoma cells specifically miR-211. Several groups have demonstrated that miR-211 as the most common miRNA expressed differentially in normal vs melanoma cells. Ectopic expression of miR-211 results in inhibition of growth and invasion of melanoma cells suggesting their role as tumor suppressor gene [20,21]. This miR-211 is encoded by a region in the sixth intron of TRPM1 (Transient Receptor Potential cation channel subfamily Member M) [22]. The level of miR-211 expression in melanoma cells has been found to be inversely proportional to the invasive potential of melanomas – with melanomas exhibiting reduced expression of miR-211 being highly invasive and vice versa [20,21,23,24]. Bell et al. have identified a new miR-211 target, NUAK1 which promotes melanoma cell adhesion [23]. Another miRNA, namely miR-196a was also shown to exhibit tumor suppressor properties as its expression was significantly reduced in malignant melanoma cells [25] (see Fig. 1).

Conversely, overexpression of several miRNA's (miR-210, miR-30b and miR-30) was seen to be upregulated in melanomas. These miRNAs are linked to stimulation of an immunosuppressive environment through cell-lysis by antigen-specific cytotoxic T lymphocytes (CTLs), changes in glycosylating proteins and increased synthesis of immunosuppressive molecules [26,27].

### 2.2. Role of miRNA in melanoma cell cycle and cell proliferation

Undifferentiated and uncontrolled cell proliferation is a hallmark of skin cancer. Cyclin dependent kinases and EF2 transcription factors are the main cell cycle regulators. Other proteins such as asc-myc, p27 and pTEN upregulate the CDKs and indirectly function as cell cycle regulators. Non-coding RNAs particularly miRNA directly target these cell cycle regulators [28–30]. let-7b is a miRNA that decreases cell proliferation by targeting cell cycle regulators by acting as a tumor suppressor gene [31]. Another miRNA-193b downregulates cyclins D1 and D2 which are responsible for uncontrolled cell growth and invasion [32]. Some miRNAs are shown to indirectly control the cell cycle through p27 and p53 tumor suppressor genes. A few studies have shown that miR221/222 directly inhibit p27 and lead to increased proliferation of melanoma cells. It has also been postulated that miR221/222 also inhibit c-kit, PTEN and TIMP3 tumor suppressor genes [33,34]. Other miRNAs such as miR205, miR149, miR18b, miR21, miR203 and miR26a have been shown to regulate cell cycle proteins through a cyclin independent manner [35].

### 2.3. Role of miRNA in tumor invasion

Multiple factors are responsible for cell migration and tumor

**Table 1**  
List of non-coding RNAs currently implicated in skin cancers.

Non-coding RNA	Target gene	Type of non-coding RNA	Expression	Skin Cancer association	References
miR-211	BRN2, KCNMA1, NFAT5, TGFBR2	microRNA	Downregulated	Melanoma	[20,21,23,45]
miR-200c	ZEB1, DEF1, Nii-2-A	microRNA	Downregulated	Melanoma	[46]
miR-210	PTPN1 TP53111, HOXA1	microRNA	Upregulated	Melanoma	[27,47,48]
miR-196a	HOX-B7, bFGF, BMP-4	microRNA	Downregulated	Melanoma	[25]
miR-30b	GALNT7	microRNA	Upregulated	Melanoma	[26,49]
Let-7a	Integrin beta 3	microRNA	Downregulated	Melanoma, BCC	[50,51]
SPRY4-IT1	n/a	Antisense long non-coding RNA	Upregulated	Melanoma	[52,53]
BANCR	CXC11	Long intergenic noncoding RNA (lincRNA)	Upregulated	Melanoma	[54]
LIME23	PSF	Long intergenic noncoding RNA (lincRNA)	Upregulated	Melanoma	[55]
ANRIL	n/a	Long intergenic noncoding RNA (lincRNA)	Upregulated	Melanoma	[56]
HOTAIR	HOXC	Long intergenic noncoding RNA (lincRNA)	Upregulated	Melanoma	[57]
miR-21	PTEN, BCL2	microRNA	Upregulated	BCC, SCC, Melanoma	[51,58–60]
miR-29c	DNMT3A and DNMT3B	microRNA	Downregulated	BCC	[61]
miR-124	ERK2	microRNA	Downregulated	SCC	[62]
miR-130a	BCL-2	microRNA	Upregulated	BCC	[61]

invasion including BSG, FSCN1,  $\beta$ 3integrin, MARKS, GALANT 7, c-met and NFK-b. Like other regulatory processes, miRNA have been shown to actively regulate the above-mentioned proteins. In a study by Segura et al., it was demonstrated that miR182 was differentially expressed in melanoma vs benign melanocytes, directly targeting proteins such as FOXO3 and MITF which contribute to migration and invasion of melanoma cells. Animal studies have demonstrated that miR182 can serve as a therapeutic target as its expression was linked to metastasis of cancer in various mouse models [36]. Another miRNA 145 is shown to downregulate FSCN1 (fascin acting bundling protein 1) which is a known regulator of cell migration and invasion [37,38].

#### 2.4. Role of long ncRNA in melanoma

Long non-coding RNA are transcribed by RNA polymerase II as an initial step which leads to formation of pri-lncRNA. This is subjected to further processing via splicing and polyadenylation which ultimately results in formation of mature-lncRNA. These mature-lncRNAs possess an intrinsic ability to interact with RNA, DNA and proteins as they can serve as tethers, decoys and scaffolds owing to their tertiary structure with surface interaction properties. Thus, lncRNA play an important role in cell regulation, proliferation and apoptosis [39–42]. Previously considered to be junk RNA, there is growing evidence of their role in skin cancers. Unlike miRNA, lncRNA has not been studied extensively and more research is needed to elucidate their specific role in cancers.

#### 2.5. Role of ncRNA in non-melanoma skin cancers

Early evidence suggests that microRNA also has a role in pathogenesis of non-melanoma skin cancers, including Basal Cell Carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) – the most common and the second most common forms of human cancers respectively. The expression levels of miRNA machinery (Drosha, DGCR8, AGO1, AGO2, PACT, and TARBP1) have been shown to be significantly higher in BCC and cSCC when compared to healthy controls [43].

The role of long non-coding RNA has also been studied in several cancers. Anticancer drug resistance has been shown to be associated with changes in expression of long non-coding RNA, suggesting a novel pathway to identify and possible reverse tumor drug resistance [44].

### 3. Conclusion

Skin cancers especially melanoma is resistant to many chemotherapeutic agents which is the main clinical barrier to improving treatment outcomes and reducing melanoma related mortality. With the increase in worldwide incidence of melanoma, it is important to find new and effective therapeutic targets. As described in this article, non-coding RNAs play a very crucial role in the pathology of skin cancers. They have both diagnostic and prognostic significance for skin cancers, and can also be a target for future therapies for cutaneous malignancies. Early diagnosis of melanoma remains the key to better treatment outcomes. There is sufficient evidence suggesting the key role of miRNA and lncRNA was early diagnostic markers. More research is needed to further utilize their potential as therapeutic targets.

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