Non-coding RNAs in skin cancers: An update

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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. There has been a recent emergence of interest in the role of non-coding RNA’s (ncRNAs) 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.

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
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 need 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-coding RNAs have garnered huge interest in the recent years regarding their role in tumorogenesis, 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, MITF, BCL2, BRAF are shown to indirectly control the cell cycle through p27 and p53 tumor suppressor genes. A few studies have shown that miR-221/222 directly inhibit p27 and lead to increased proliferation of melanoma cells [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 [20,21,24]. 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-my c, 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 proteins. Other 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).

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2.3. Role of miRNA in tumor invasion

Multiple factors are responsible for cell migration and tumor

**Table 1**

| Non-coding RNA | Target gene          | Type of non-coding RNA | Expression       | Skin Cancer association | References |
|----------------|----------------------|------------------------|------------------|-------------------------|------------|
| miR-211        | BRN2, KCNMA1, NFAT5, TGFB2 | microRNA               | Downregulated    | Melanoma               | [20,21,23,45] |
| miR-200c       | ZEB1, DEFI, Nil-2-A   | microRNA               | Downregulated    | Melanoma               | [46]        |
| miR-210        | PTEN1, TP53, TFRA1    | 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 (lncRNA) | Upregulated | Melanoma               | [52,53]     |
| BANCR          | CXCR1                | Long intergenic noncoding RNA (lncRNA) | Upregulated | Melanoma               | [54]        |
| LIME23         | PSF                  | Long intergenic noncoding RNA (lncRNA) | Upregulated | Melanoma               | [55]        |
| ANKIR          | n/a                  | Long intergenic noncoding RNA (lncRNA) | Upregulated | Melanoma               | [56]        |
| HOTAIR         | HOXC                 | Long intergenic noncoding RNA (lncRNA) | 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, β3integrin, 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 are differentially expressed in melanoma vs benign melanocytes, met and NFK-b. Like other regulatory processes, miRNA have been shown to be significantly involved in cancers respectively. The expression levels of miRNA machinery are the most common and the second most common forms of human malignancies. Skin cancers especially melanoma is resistant to many chemotherapy 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 IncRNA in early diagnostic markers. More research is needed to further utilize their potential as therapeutic targets.

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