Role of non-coding RNAs in UV-induced radiation effects (Review)

XIAOFEI LIANG[1], CHAO ZHANG[1], LIJUAN SHEN[2], LING DING[1] and HAIPENG GUO[1]

[1]Department of Laboratory Medicine, The First Hospital of Qiqihar, Qiqihar, Heilongjiang 161000, P.R. China;
[2]Department of Laboratory Medicine, Qiqihar MingZhu Hospital, Qiqihar, Heilongjiang 161000, P.R. China

Received December 18, 2023; Accepted April 4, 2024

DOI: 10.3892/etm.2024.12550

Abstract. Ultraviolet (UV) is divided into UVA (long-wave, 320-400 nm), UVB (middle-wave, 280-320 nm) and UVC (short-wave, 100-280 nm) based on wavelength. UV radiation (UVR) from sunlight (UVA + UVB) is a major cause of skin photodamage including skin inflammation, aging and pigmentation. Accidental exposure to UVC burns the skin and induces skin cancer. In addition to the skin, UV radiation can also impair visual function. Non-coding RNAs (ncRNAs) are a class of functional RNAs that do not have coding activity but can control cellular processes at the post-transcriptional level, including microRNA (miRNA), long non-coding RNA (lncRNA) and circulatory RNA (circRNA). Through a review of the literature, it was determined that UVR can affect the expression of various ncRNAs, and that this regulation may be wavelength specific. Functionally, ncRNAs participate in the regulation of photodamage through various pathways and play pathogenic or protective regulatory roles. In addition, ncRNAs that are upregulated or downregulated by UVR can serve as biomarkers for UV-induced diseases, aiding in diagnosis and prognosis assessment. Therapeutic strategies targeting ncRNAs, including the use of natural drugs and their extracts, have shown protective effects against UV-induced photodamage. In the present review, an extensive summarization of previous studies was performed and the role and mechanism of ncRNAs in UV-induced radiation effects was reviewed to aid in the diagnosis and treatment of UV-related diseases.

Contents

1. Introduction
2. Effect of UVR on ncRNAs expression
3. Role of ncRNAs in UV-induced photodamage
4. Role of ncRNAs in UV-induced photoaging
5. Role of ncRNAs in UV-induced pigmentation
6. Role of ncRNAs in UV-induced skin cancer
7. Role of ncRNAs in UV-induced ocular diseases
8. Application of biological therapy targeting ncRNA in UV-induced radiation effect
9. Summary

Correspondence to: Professor Haipeng Guo, Department of Laboratory Medicine, The First Hospital of Qiqihar, 700 Bukui South Street, Qiqihar, Heilongjiang 161000, P.R. China
E-mail: tgzyyx_lxf@163.com

Key words: non-coding RNA, microRNA, long non-coding RNA, circular RNA, ultraviolet

1. Introduction

The primary source of ultraviolet radiation (UVR) in the environment is sunlight, of which 95% is UVA and 5% is UVB (1). UVA radiation can modify the immune response of mammalian cells, which may be beneficial in inflammatory and autoimmune diseases but is detrimental to skin aging and skin cancer. UVB can penetrate the epidermis and reach the dermal surface, and UVB exposure leads to severe cellular stress and pigmentation (2). UVC radiation primarily occurs during accidental exposure to UV disinfection, which can burn the skin during short-term exposure. Long-term or high-intensity exposure can cause skin cancer (3). In addition to the skin system, UVR can damage visual function in humans and animals, causing lens opacity, abnormal expression of retinal transcriptome genes, and decreased volume of corneal epithelial cells (4). The UV stress response is generated in skin cells in response to UVR damage, maintaining the integrity of the genome through DNA repair systems and cell cycle checkpoints in eukaryotic cells. Failure of this response may cause immunosuppression, inflammation, photoaging and carcinogenesis in the human skin. Following UVR exposure, the expression of protein-coding genes is altered to coordinate these injury responses (5).

The DNA damage response (DDR) under UVR requires a complex cellular event network involved in the maintenance of intracellular homeostasis and genome stability, including non-coding RNAs (ncRNAs) (6). In the human genome, 76% of the genes can be transcribed into RNA; however, only 2.94% have protein-coding functions, most of which are ncRNAs (7). There are several types of ncRNAs, including microRNAs (miRNAs or miRs), long non-coding RNA (lncRNAs) and circular RNA (circRNAs) (8). Because UV exposure is unavoidable, it is necessary to understand the underlying molecular mechanisms of UV-induced damage to develop effective treatments. In previous years, ncRNAs have been shown to be involved in the regulation of protein transcription and post-translational modifications caused by

UVR. For the first time, the role of miRNAs in UV-induced skin-related diseases were summarized the findings of several studies involving lncRNAs and circRNAs were discussed in the present review. The role of these ncRNAs in UV-induced ocular diseases, which has not been previously discussed in detail, has also been summarized. An in-depth understanding of the regulatory mechanisms of ncRNAs in UV-induced diseases will help design and optimize targeted therapies for the prevention and treatment of skin diseases and visual impairment.

2. Effect of UVR on ncRNAs expression

UVR can regulate the expression of a variety of ncRNAs (9-14); however, the effects of different UVR wavelengths on the same ncRNA differ. Kraemer *et al* (15) reported that most differentially expressed miRNAs in human primary keratinocytes irradiated with UVA and UVB changed in the same direction; however, miR-96 responded differently to UVA (+1.7-fold) and UVB (-3.5-fold). The present study is the first to demonstrate the differential miRNA response to UVA and UVB in human primary keratinocytes, suggesting that selective regulation of signaling pathways occurs in response to different UV energies. Zhang *et al* (16) showed that the expression of miR-27a was upregulated only in UVB-irradiated fibroblasts and that UVA irradiation had no effect. Yo and Rünger (17) performed a genome-wide analysis of lncRNAs in human skin fibroblasts after exposure to UVR. Venn diagrams revealed that most lncRNAs were affected only by UVA or UVB, and only a few lncRNAs were upregulated or downregulated by both, indicating that cells respond to UVA and UVB in notably different manners. However, miR-340 is highly expressed in ARPE-19 cells treated with 60 mJ/cm^2 UVB (18) and poorly expressed in Pig-1 cells treated with 100 mJ/cm^2 UVB (19), suggesting that the effect of UVR on ncRNAs is also related to other factors. Chen *et al* (20) analyzed the effect of UVR by different quality (UVA, UVB, and UVA + UVB) on the miRNA expression pattern in primary and metastatic cSCCs (Met-1, Met-4) cell lines through the NanoString nCounter platform (https://nanostring.com/products/ncounter-analysis-system/ncounter-systems-overview/). The results of the aforementioned study indicated that the expression pattern of miRNAs depends on both the cell line used and the quality of the UVR. As the influence of UVR on ncRNAs may be wavelength-specific, the effects of different types of UVR on ncRNA expression and function in the following sections were summarized.

Effect of UVA on ncRNA expression. UVA generally does not cause acute skin inflammation but has an irreversible cumulative effect on skin damage (21). Repeated UVR exposure can improve simulation of the effects of long-term UVR exposure. Zheng *et al* (22) discovered that 1,730 lncRNAs exhibited >2-fold expression changes in human dermal fibroblasts (HDFs) repeatedly irradiated with UVA, of which 1,494 were upregulated and 236 were downregulated. Predicted targets of these differentially expressed lncRNAs were associated with skin photoaging, including TGF-β signaling pathways and collagen fiber metabolism. In a recent study (23), it was observed that 34 miRNAs were differentially expressed (>1.5-fold) in HDFs exposed to repeated UVA irradiation. The miRNA-lncRNA-mRNA-signal transduction pathway analysis revealed that the TNF signaling pathway, the thyroid hormone signaling pathway and lysosomes were affected after UVA irradiation. The aforementioned research was helpful for further understanding the delicate interplay of gene regulation at the ncRNA level in repeated UVA-induced skin photoaging and skin cancer.

Pathogen reduction technologies (PRTs), such as the intercept (amotosalen + UVA) and mirasol (riboflavin + UVB), hold promise for improving the safety of blood storage and prolonging its shelf life; however, these PRTs may affect the quality and function of platelets (24). Arnason *et al* (25) showed that among 25 miRNAs detected in intercept-treated platelets, only five miRNAs had regulatory changes. It was concluded that this treatment was safe and did not significantly alter the miRNA profile of the platelets produced and stored under standard blood banking conditions. However, Osman *et al* (26) reported that platelets treated with the intercept demonstrated decreased levels of six miRNAs compared with platelets stored in plasma. However, treatment of platelets with mirasol did not induce these effects. Interestingly, Diallo *et al* (27) observed specific miRNAs in platelet-released microparticles (MPs), which were impaired after treatment with the intercept or its additive solution (SSP$^+$). Similarly, mirasol had no effect on the miRNA profile of platelet-derived MPs compared with that of the control group. However, Ye *et al* (28) revealed that platelets treated with mirasol differentially expressed a variety of miRNAs considered to play functional roles in energy homeostasis, cell communication, proliferation, migration and apoptosis.

Effect of UVB on ncRNA expression. Narrow-band UVB (NB-UVB) phototherapy has demonstrated favorable clinical efficacy for the treatment of a range of diverse skin diseases, such as psoriasis and vitiligo. NB-UVB phototherapy can promote melanin synthesis and increase tyrosinase activity in melanocytes; however, the specific mechanism remains unclear (29). Soonthornchai *et al* (30) observed that miR-155 was highly expressed in psoriatic skin lesions and that NB-UVB phototherapy significantly reduced miR-155 expression. In another study (31), miR-378a-3p was reported to be overexpressed in skin biopsies of active psoriatic lesions, whereas its expression was significantly reduced after NB-UVB phototherapy. In addition, it was identified that miR-378a-3p disrupts cell cycle progression, resulting in cell cycle arrest at the G1 phase in an *in vitro* keratinocyte model. Ele-Refaei and El-Esawy (32) discovered that the level of miR-146a in the blood of patients with psoriasis was higher than that in healthy controls and was significantly reduced after 12 weeks of NB-UVB phototherapy. Parihar *et al* (33) detected increased expression of miR-16 and miR-145 in the peripheral blood mononuclear cells, serum and lesional skin of patients with active non-segmental generalized vitiligo, whereas both were decreased after NB-UVB treatment. These findings provide a mechanistic model in which miRNAs are involved in the pathogenesis of psoriasis and vitiligo, and NB-UVB induces re-pigmentation by altering miRNA levels and enhancing the expression of pigment-associated genes.

Effect of UVC on ncRNA expression. To maintain genome integrity, a network of DDR mechanisms is required (34). Although numerous coding genes have been reported to be involved in UV-induced DDR (UV-DDR), the exact function of ncRNA in UV-DDR remains unclear. Williamson *et al* (35) reported that UVC radiation can induce ncRNAs that are functionally antagonistic to proteins encoded by the same gene. ASCC3 expresses both coding and non-coding transcript isoforms with opposite effects on transcription recovery after UVC-induced DNA damage. Liu *et al* (36) examined UV-induced gene expression in human fibroblasts using RNA sequencing (RNA-seq) with fractionated chromatin-associated and cytoplasmic transcripts. Unlike protein-coding genes with shorter transcripts, which preferentially recovered after UVC irradiation, the repression of lncRNA transcription was first inactivated in longer non-coding transcripts. These studies provide useful information to understand how cells respond to transcription-blocking DNA damage. An integrated analysis of lncRNA and mRNA expression profiles in UVC-irradiated human lymphocytes was performed by Xu *et al* (37). The results revealed that the upregulated lncRNAs were more common than the downregulated lncRNAs with increasing radiation doses. Using Cytoscape (https://cytoscape.org/), five lncRNAs and 13 genes co-expressed with p53 were screened, which may be involved in the regulation of DNA damage, cell cycle arrest and cell death. These results revealed that lncRNAs may play a role in UVC-induced DDR by regulating gene expression in the p53 signaling pathway.

3. Role of ncRNAs in UV-induced photodamage

Role of miRNAs in UV-induced photodamage. Although the complex mechanism of skin damage caused by UV exposure is not fully understood, the available data suggest that it is closely related to apoptosis and inflammatory responses. Signal transducer and activator of transcription 3 (STAT3) is a well-known anti-apoptotic factor (38). Liao *et al* (39) reported that STAT3 can inhibit UV-induced DNA damage and increase the expression of ataxia telangiectasia-mutated (ATM) and Rad3-related (ATR) genes in A431 cells by activating the transcription of the ATR promoter. Notably, miRNA-383 can inhibit ATR expression by targeting its 3' untranslated region (UTR) in A431 cells; however, STAT3 can downregulate the transcription of miR-383 promoter to exert anti-apoptotic effects. Interestingly, Chowdhari and Saini (40) revealed that STAT3 is a target of psoralen and UVA (PUVA)-induced miR-4516 in HaCaT cells, as confirmed by luciferase reporter gene assays and western blotting. Additionally, anti-miR-4516 treatment partially inhibited PUVA-induced apoptosis. To elucidate the mechanism of action of miR-4516 in PUVA-induced apoptosis, transcriptomic changes were investigated using an Illumina genome-wide gene expression bead chip. It was demonstrated that miR-4516-mediated downregulation of the ubiquitin-conjugating enzyme 2N may contribute to p53 nuclear translocation and its activation, and that the pro-apoptotic activity of PUVA is mediated by retinoic acid-inducible gene 1 and is dependent on the activation of p53 and NF-κB (41).

Oncoprotein c-Myc is critical for cell homeostasis and is downregulated upon exposure to several types of stress, including UV-induced DNA damage (42). However, the mechanism through which UV radiation induces c-Myc reduction remains unclear. Li *et al* (43) demonstrated that miR-130a could target the 3'UTR of c-Myc mRNA to suppress its expression and inhibit cell proliferation in response to UV irradiation. Furthermore, inhibition of miR-130a significantly inhibited the UV-mediated reduction of c-Myc. Zhang *et al* (44) reported that the upregulation of miR-26a under UVB irradiation promotes HaCaT cell apoptosis by targeting the histone methyltransferase EZH2. Additionally, the UVB/miR-26a/EZH2 regulatory axis is largely dependent on the expression level of Myc. Degueurce *et al* (45) described a novel PPARβ/δ-dependent molecular cascade involving transforming growth factor β1 (TGF-β1) and miR-21, which was activated in the UV-irradiated epidermis. As a novel UV-induced miRNA in the epidermis, miR-21-3p plays a pro-inflammatory role in keratinocytes, and its high expression in the human skin is related to psoriasis and squamous cell carcinoma. Inhibition of miR-21-3p in human skin biopsies reduced UV-induced cutaneous inflammation *in vitro*, which was dependent on TGF-β1 receptor activation. Ni *et al* (46) identified that exosome-mediated transfer of miR-769-5p could act as an intercellular messenger that exacerbates UV-induced bystander effects in human skin fibroblasts, such as decreased proliferation, increased oxidative damage and accelerated apoptosis. Mechanistically, miR-769-5p may downregulate TGF-β1 expression by targeting its 3' UTR. Jiang *et al* (47) reported that UVA reduced SIRT1 protein levels in skin fibroblasts in a time-dependent manner and that miR-27a-5p was upregulated after SIRT1 knockdown. In addition, SIRT1 downregulation or miR-27a-5p overexpression resulted in increased expression of MMP1 and decreased expression of COL1 and BCL2 expression. This treatment increased cell apoptosis and also induced cell arrest in the G2/M phase. Yang *et al* (48) suggested that UVB may promote inflammation and the expression of oxidative stress signals by upregulating miR-4497 expression in keratinocytes, thereby mediating cell damage.

miRNAs promote as well as inhibit UV-induced apoptosis. UVB irradiation significantly enhances si-IL-6-induced HaCaT cell damage and promotes apoptosis. However, overexpression of miR-139-5p attenuates UVB-induced damage by inactivating the Notch and PI3K/AKT pathways and downregulating Toll-like receptor 4 (TLR4) (49). Zhang *et al* (50) revealed that miR-27a is significantly upregulated in HaCaT cells after UVB irradiation, removing CPDs and decreasing apoptosis. miR-27a directly reduced the expression and luciferase activity of target genes such as transactive response DNA-binding protein and apoptotic protease activating factor-1. A significant increase in miR-664 expression was observed in UVB-irradiated HaCaT cells, and overexpression of miR-664 promoted cell viability and inhibited UVB-induced apoptosis (51). Furthermore, the loss or gain of armadillo-repeat-containing protein 8 can rescue/block the effect of miR-664 on UVB-induced HaCaT cell proliferation. Tu *et al* (52) revealed that miR-31-3p induced by UVA and UVB was correlated with the severity of chronic actinic dermatitis, which affects the permeability barrier of keratinocytes by targeting Claudin 1CLDN1. Another study (53) revealed that miR-221-3p expression was significantly upregulated, whereas

fos proto-oncogene, AP-1 transcription factor subunit (FOS) expression was downregulated in UVB-irradiated skin tissues from patients with coronary artery disease. A dual-luciferase reporter assay showed that miR-221-3p targeted the 3' UTR of FOS, and western blotting confirmed that miR-221-3p can negatively regulate FOS, thereby regulating Bcl-xl/Bax. Furthermore, miR-221-3p overexpression or FOS knockdown promoted cell proliferation and reduced apoptosis; however, these effects were reversed by a Bcl-xl inhibitor.

Role of lncRNA in UV-induced photodamage. The UV-induced apoptotic response is considered to be regulated by lncRNAs at the post-transcriptional level; however, the specific mechanism underlying this process remains unclear. Rünger and Yo (54) demonstrated that the lncRNA GS1-600G8.5 is a key regulator of IL-8 in keratinocytes and fibroblasts, as knockdown of GS1-600G8.5 eliminated UVA-induced upregulation at the mRNA level. Zhang *et al* (55) observed the overexpression of lncRNA Meg3 after UVB irradiation in primary murine skin fibroblasts, and the upregulation of Meg3 expression was associated with the activation of inflammatory cytokines. Silencing Meg3 can inhibit the expression of cytokines (*in vitro*) and UVB-induced skin lesions (*in vivo*). Furthermore, Meg3 functioned as a competitive endogenous RNA (ceRNA) that acts as a sponge for miR-93-5p, thereby regulating epiregulin expression. Liang and Hu (56) revealed that lncRNA HOTTIP levels were significantly increased after UV stimulation in GC-1 cells (a spermatogonia germ cell line) and that HOTTIP regulated the cellular response to UV radiation through the coordinated activation of its neighbouring gene homeobox A13 (Hoxa13). HOTTIP and Hoxa13 regulate UV-induced G2/M phase arrest and early apoptosis. Interestingly, HOTTIP can upregulate the expression of p53 through Hoxa13, and p53 which in turn regulates the expression of both HOTTIP and Hoxa13. Collectively, the aforementioned study provided new insights into the functions of lncRNAs in response to UV damage in spermatogenic cells.

nc886 is a lncRNA that is also known as a vault RNA or miRNA precursor. The two RNA-binding sites of protein kinase RNA-activated (PKR) are located in the central region of the stable structure of nc886, and successful binding leads to decreased PKR activity (57). Lee *et al* (58) reported that nc886 expression is reduced in UVB-irradiated skin cells, resulting in uncontrolled PKR activity. Increased expression of the inflammatory cytokines, MMP-9, COX-2, and type IV collagenase ultimately accelerates the inflammatory response and skin aging. Another study (59) elucidated the regulatory mechanism by which UVB irradiation accelerates the methylation of nc886 and reduces its expression. Mechanistically, PKR activation is induced to accelerate the expression of MMP-9 and COX-2 as well as the release of certain pro-inflammatory cytokines, especially IL-8 and TNF-α. By contrast, the expression and production of these inflammatory factors was inhibited in the nc886-overexpressed model. Furthermore, in a model of replicative, senescent fibroblasts, nc886 expression decreased, whereas that of methylated nc886 increased. AbsoluTea Concentrate 2.0 increases nc886 expression and ameliorates fibroblast senescence by inhibiting age-related biomarkers (60). These results suggest that nc886 has potential as a novel anti-aging (Table I).

4. Role of ncRNAs in UV-induced photoaging

Role of miRNAs in UV-induced photoaging. Exposure to solar UV accelerates skin aging; however, the molecular mechanisms through which chronic UVB exposure affects the skin biomechanical properties have not been well characterized. Lang *et al* (61) revealed that SIRT4 upregulation was associated with decreased miR-15b levels in all models of dermal cells undergoing replicative or stress-induced senescence triggered by UVB, as miR-15b targets one of the functional binding sites in the SIRT4 gene. In addition, inhibition of miR-15b in a SIRT4-dependent manner increased the production of mitochondrial ROS and modulated the components of the senescence-associated secretory phenotype. Therefore, miR-15b acts as a negative regulator of UVB stress-induced SIRT4 expression, thereby antagonizing senescence-related mitochondrial dysfunction. Unlike SIRT4, SIRT6 is an established antiaging protein that regulates collagen metabolism. Joo *et al* (62) revealed that miR-378b expression was increased in a dose-dependent manner in HDFs, and that was negatively strongly related to the mRNA level of collagen type I α1 (COL1A1). Furthermore, the downregulation of miR-378b enhanced COL1A1 mRNA expression in HDFs. Target analysis of miR-378b revealed that the regulator of COL1A1, SIRT6, contained a target sequence of miR-378b in its 3'UTR. Collectively, the aforementioned study demonstrates that miR-378b is involved in UVB-induced aging of HDFs by inhibiting the mRNA expression of COL1A1 via interference with SIRT6. Blackstone *et al* (63) revealed that following UVB irradiation, the diameter of dermal collagen fibrils was significantly decreased and the expression of miR-34 family was increased; it was considered that miRNAs may play an important role in controlling extracellular matrix deposition and skin biomechanics after long-term UVB exposure. A study by Li *et al* (64) revealed that increased miR-183 expression after UVC exposure may inhibit the cell cycle through multiple gene targets, thus promoting cell aging. A previous study suggested that the role of miRNAs in UV-induced skin aging may depend on the intracellular miRNA content after irradiation and not before irradiation. Ishihara *et al* (65) transfected miR-520d-5p into NHDFs using a lentivirus, either before or after UVB irradiation. The results revealed that NHDFs transfected with miR-520d-5p before UVB irradiation demonstrated apoptotic characteristics, and such transfection had no preventive effects. However, transfection after UVB exposure can induce the reprogramming of damaged fibroblasts and enable the survival of CD105-positive cells. Mechanistically, miR-520d-5p restored CD105-positive cells to their normal senescent state by activating the c-Abl-ATR-BRCA1 pathway, upregulating p53, and inducing demethylation. The aforementioned study demonstrated that supplementation with exogenous miRNAs has a remedial effect on UVR-induced skin photoaging.

Role of lncRNA in UV-induced photoaging. MALAT1 plays an important role in the occurrence and development of tumors as well as cardiovascular and neurological diseases; however, its impact on photoaging remains to be elucidated (66). Lei *et al* (67) revealed that MALAT1 expression increased in UVB-irradiated fibroblasts, accompanied

Table I. Role of non-coding RNAs in UV-induced photodamage.

ncRNAs	UV type	Dose	Alteration	Cells/Tissues	Targeted molecules	Mechanisms and pathways	(Refs.)
miR-383	Unknown	20 J/m^2	↑	A431	ATR	Promoting apoptosis	(39)
miR-4516	UVA	1.2 J/cm^2	↑	HaCaT	STAT3	Promoting apoptosis	(40)
miR-4516	UVA	1.2 J/cm^2	↑	HaCaT	UBE2N	Promoting apoptosis	(41)
miR-130a	UVC	40 J/m^2	↑	Hek ;U2OS	c-Myc	Inhibiting proliferation	(43)
miR-26a	UVB	30 mJ/cm^2	↑	HaCaT	EZH2	Promoting apoptosis	(44)
miR-21-3p	UVB	120 mJ/cm^2	↑	HaCaT	TGF-β1	Promoting inflammation	(45)
miR-769-5p	UVA+UVB	Unknown	↑	HSFs	TGF-β1	Inducing bystander effect	(46)
miR-27a-5p	UVA	5 J/cm^2	↑	HDFs	MMP1; COL1; BCL2	Promoting apoptosis and aging	(47)
miR-4497	UVB	40 mJ/cm^2	↑	HaCaT	NF-κB	Promoting inflammation	(48)
miR-139-5p	UVB	30 mJ/cm^2	↑	HaCaT	TLR4	Inhibiting apoptosis	(49)
miR-27a	UVB	30 mJ/cm^2	↑	HaCaT	TARDBP; APAF-1	Inhibiting apoptosis	(50)
miR-664	UVB	30 mJ/cm^2	↑	HaCaT	ARMC8	Inhibiting apoptosis	(51)
miR-31-3p	UVA+UVB	2 J/cm^2+20 mJ/cm^2	↑	HaCaT	CLDN1	Permeability barrier	(52)
miR-221-3p	UVB	0-30 mJ/cm^2	↑	HaCaT	FOS	Promoting proliferation	(53)
lncRNA GS1-600G8.5	UVB	200 kJ/m^2	↑	Fibroblasts; keratinocytes	IL-8	Promoting inflammation	(54)
lncRNA Meg3	UVB	100 mJ/cm^2	↑	HDFs	miR-93-5p; Ereg	Promoting inflammation	(55)
lncRNA HOTTIP	UVC	0-10 J/m^2	↑	GC-1	Hoxa13	Promoting apoptosis	(56)
lncRNA nc886	UVB	20 mJ/cm^2	↓	HaCaT	PKR	Inhibiting inflammation	(59)
lncRNA nc886	UVB	0-10 mJ/cm^2	↓	HaCaT	PKR	Inhibiting inflammation	(60)

UV, ultraviolet; nc, non-coding; MiR, microRNA; lnc, long non-coding; ATP, Rad3-related; UBE2N, ubiquitin conjugating enzyme E2 N; c-Myc, myc proto-oncogene, bhlh transcription factor; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; MMP1, matrix metallopeptidase 1; COL1, collagen type I; BCL2, BCL2 apoptosis regulator; TLR4, Toll-like receptor 4; TARDBP, transactive response DNA-binding protein; APAF-1, apoptotic protease activating factor-1; ARMC8, armadillo-repeat-containing; CLDN1, Claudin 1; FOS, fos proto-oncogene, AP-1 transcription factor subunit; Hoxa13, homeobox A13; PKR, protein kinase RNA-activated.

by an increase in the number of senescent cells. Notably, UVB-induced MALAT1 expression was independent of ROS generation. Increased MMP-1 expression and phosphorylation of extracellular signal-regulated kinase (ERK), p38, and Jun N-terminal kinase (JNK) were observed in photoaged fibroblasts; however, these effects were reversed by MALAT1 silencing. Therefore, it was hypothesized that MALAT1 may be involved in UVB-induced photoaging by regulating the ERK/mitogen-activated protein kinase signaling pathway. MALAT1 was identified as a negative upstream regulator of miR-211, the most significantly downregulated miRNA in the UV-induced photodamaged epidermis (11). MALAT1 overexpression results in increased SIRT1 expression and removal of UVB-induced CPDs in primary keratinocytes. These results establish a novel MALAT1-miR-211-SIRT1 signaling axis that may provide protection against amelanotic keratinocytes in vitiligo.

LncSPRY4-IT1, a broadly expressed lncRNA, increased by 1.66±0.23-fold in UVA-irradiated fibroblasts as reported by Hou *et al* (68). LncSPRY4-IT1-targeting proteins are involved in biological regulation during the skin photoaging process, and KEGG analysis showed that these targeted proteins were primarily enriched in metabolic processes. The formation of this lncRNA-protein regulatory network may serve as a novel upstream intervention target for photoaging-related skin diseases. Li *et al* (69) revealed that the knockdown of RP11-670E13.6, an upregulated lncRNA in UVB-irradiated HDFs, promoted a robust senescence phenotype. Furthermore, RP11-670E13.6 delayed cellular senescence through the p16-pRB senescence pathway in UVB-irradiated HDFs. Another study (70) revealed that RP11-670E13.6, which directly binds to miR-663a, acts as a sponge for miR-663a to regulate the activation of Cdk4 and Cdk6, thus delaying the senescence of skin cells induced by UV irradiation. In addition, it was also discovered that RP11-670E13.6 may promote DNA damage repair by increasing the level of ATM and γH2AX. These findings indicated that the RP11-670E13.6/miR-663a/CDK4 (CDK6) axis, which may function as a ceRNA network, plays an important role in UVB-induced cellular senescence.

Role of circRNA in UV-induced photoaging. circRNA is a newly discovered ncRNA that exerts regulatory effects by sequestering miRNAs, such as sponges. Peng *et al* (71) identified 29 differentially expressed circRNAs in UVA-irradiated HDF, of which 12 were upregulated and 17 were downregulated. Among the downregulated circRNAs, circCOL3A1-859267 was the most notably altered. Overexpression of circCOL3A1-859267 inhibited the decrease in type I collagen expression induced by UVA, and its silencing reduced the intensity of type I collagen staining. Through bioinformatic analysis, 44 miRNAs were predicted to bind to circol3A1-859267, five of which (miR-29a, miR-29b, miR-29c, miR-767 and miR-133a) may interact with type I collagen. Using a dual-luciferase reporter assay, it was confirmed that only miR-29c binds to circCOL3A1-859267 (72). In UVA-irradiated HDFs, only miR-29c expression was upregulated. The aforementioned findings suggested that circCOL3A1-859267 regulates the expression of type I collagen in HDFs by sponging and sequestering miR-29c, which may be a novel target for interfering with UVR-induced photoaging. Another study analyzed circRNA expression in UVA-irradiated HDFs (73). A total of 128 circRNAs, including 89 downregulated and 39 upregulated circRNAs, were differentially expressed following UVA irradiation. The same cells and experimental methods as those of Peng *et al* (71) were used; however, the circRNAs differentially expressed were not exactly the same. It was identified miRNAs that may be sponged by downregulated circ-0011129 using the Arraystar proprietary miRNA target prediction software (https://www.arraystar.com/reviews/cooperative-mirna-target-prediction-and-go--pathway-analysis/) and TargetScan (https://www.targetscan.org/vert_80/), including miR-484, miR-3619-5p and miR-6732-5p, which share binding sites with photoaging-related proteins, such as COL1A1, COL3A1 and elastin. Si *et al* (10) identified 472 differentially expressed circRNAs in a UVB stress-induced premature senescence (UVB-SIPS) model of human fibroblasts, and reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis confirmed that circRNA-100797 was downregulated in UVB-SIPS. Overexpression of circRNA-100797 accelerates cell proliferation and alleviates cell cycle arrest. In addition, the luciferase reporter assay revealed that circRNA-100797 could target miR-23a-5p, and that miR-23a-5p upregulation blocked the photoprotective effect of circRNA-100797 overexpression in UVB-SIPS (Table II).

5. Role of ncRNAs in UV-induced pigmentation

Role of miRNAs in UV-induced pigmentation. The effect of UVR on melanin production is well established; however, the molecular and cellular mechanisms that control pigmentation remain incompletely understood. Using mathematical modelling and empirical studies, Malcov-Brog *et al* (74) showed that the UVB-induced melanocyte master regulator melanocyte-inducing transcription factor (MITF) serves to synchronize the stress response and pigmentation. MITF oscillation is regulated through multiple negative regulatory loops: One at the transcriptional level involving HIF1-α and another at the post-transcriptional level involving miRNA-148a. Jian *et al* (75) investigated the expression of miRNAs in melanocytes upon UVB irradiation using microarray screening and found that miR-340 expression was increased 4.87-fold. The upregulation of miR-340 promotes the formation of dendrites and the transport of melanosomes, thereby inhibiting UVB-induced pigmentation. Furthermore, a luciferase reporter assay showed that miR-340 directly targets Ras homolog family member A (RhoA) in Pig1, an immortalized human melanocyte cell line. Another study (19) by this group revealed that miR-340 expression was found to increase in Pig1 cells after UVB irradiation, which was negatively correlated with MITF expression. Overexpression of miR-340 reduces the amount of melanin and inhibits the expression of several critical molecules in the pigment synthesis pathway, whereas miR-340 knockdown yields the opposite results. Lin *et al* (76) reported that UVA irradiation induces the melanogenesis signaling pathway by increasing the production of melanin and the number of A375.S2 cells. Similarly, UVA irradiation increased the expression of α-MSH and decreased the melanogenesis-regulating signal, such as the phosphorylation of Akt and epidermal growth factor receptor (EGFR). However, miR-21 overexpression reduced the expression of α-MSH and increased the phosphorylation of Akt and EGFR in UVA-irradiated A375.S2 cells. Moreover, miR-21 expression in UVA-induced melanogenesis is downregulated by gefitinib, an inhibitor of Akt and EGFR. These results indicated that the inhibitory activity of miR-21 on the melanogenesis induced by UVA may be related to the downregulation of α-MSH and the activation of Akt and EGFR.

UV-induced pigmentation is also mediated by extracellular vesicles (EVs), exosomes, or their miRNAs. Overexpression of miR-203 and miR-3196 in exosomes secreted by black and Caucasian keratinocytes, respectively, is the primary cause of pigmentation in the two types of keratinocytes, both of which are regulated by UVB (77). EVs purified from UVA-irradiated human primary melanocytes were added to keratinocytes, resulting in the activation of TGF-β and IL-6/STAT3 signaling pathways in keratinocytes (78). This EV-mediated crosstalk between melanocytes and keratinocytes may be related to the activation of proliferation and anti-apoptotic signaling by miR-21. Zhang *et al* (79) revealed that caveolae were asymmetrically distributed in melanocytes and were particularly abundant at the melanocyte-keratinocyte interface in the epidermis. Furthermore, caveolae in melanocytes are positively regulated by UVR and keratinocyte-released factors, such as miR-203a, suggesting that the coordination of intercellular communication is crucial to skin pigmentation. Shen *et al* (80) first confirmed that UVB radiation can enhance the secretion of exosomes by melanocytes and alter their exosomal miRNA profiles. A total of 15 miRNAs were more abundant in UVB-irradiated melanocyte-derived exosomes than in non-irradiated ones. The aforementioned study introduced a novel direction for investigating the communication between melanocytes and other skin cells as well as the relationship between UVB radiation and the initiation of skin malignancy. Sha *et al* (81) reported that physiological doses of UVR (UVA + UVB) induced quiescent melanocytes to enter a senescent-like state *in vitro*. Furthermore, these irradiated cells secreted exosomes with specific miRNAs that differed in quantity from those in unirradiated melanocytes. Therefore, miRNAs are released from melanocytes by exosomes following UVR-induced premature senescence.

Table II. Role of ncRNAs in UV-induced photoaging.

ncRNAs	UV type	Dose	Alteration	Cells/Tissues	Targeted molecules	Mechanisms and pathways	(Refs.)
miR-23a	UVA + UVB	9 J/cm^2+ 25 mJ/cm^2	↑	HDFs	AMBRA1	Inhibiting autophagy	(16)
miR-15b	UVB	100 J/m^2	↓	HDFs	SIRT4	Decreasing mitochondrial ROS	(61)
miR-378b	UVB	5-25 mJ/cm^2	↑	HDFs	SIRT6	Decreasing COL1A1	(62)
miR-34	UVB	745-5227 J/m^2	↑	Skin (SKH1 hairless mice)	Unknown	Dysregulating collagen structure	(63)
miR-183	UVC	10 J/m^2	↑	HTMs; HDF; HeLa	KIAA0101	Inhibiting cell cycle	(64)
miR-124	UVB	5 and 10 mJ/cm^2	↑	NHEKs	SA-gal	Promoting senescence	(99)
lncRNA MALAT1	UVB	60 mJ/cm^2	↑	HaCaT	MMP-1	Activating ERK/MAPK pathway	(67)
lncRNA MALAT1	UVB	10 mJ/cm^2	↑	HaCaT	SIRT1	MALAT1-miR-211-SIRT1 axis	(11)
lncRNA LncSPRY4-IT1	UVA	10 J/cm^2	↑	HDFs	Unknown	Regulating metabolic process	(68)
lncRNA RP11-670E13.6	UVB	40 mJ/cm^2	↑	HDFs	p16-pRB	Inhibiting senescence	(69)
lncRNA RP11-670E13.6	UVB	40 mJ/cm^2	↑	HDFs	miR-663a; Cdk4; Cdk6	miR-663a/CDK4 (CDK6) axis	(70)
circRNA 7 Circol3A1-85926	UVA	10 J/cm^2	↓	HDFs	Type I collagen	Increasing collagen expression	(71)
circRNA Circol3A1-859267	UVA	10 J/cm^2	↓	HDFs	miR-29c; type I collagen	miR-29c/type I collagen axis	(72)
circRNA Circ-0011129	UVA	10 J/cm^2	↓	HDFs	COL1A1; COL3A1	Regulating photoaging-related protein	(73)
circRNA-100797	UVB	10 mJ/cm^2	↓	HDFs	miR-23a-5p	Alleviating cell cycle arrest	(10)

Nc, non-coding; UV, ultraviolet; miR, microRNA; lnc, long non-coding; circ, circular; AMBRA1, autophagy and beclin 1 regulator 1; SIRT, sirtuin; KIAA0101, PCNA Clamp Associated Factor; MMP1, Matrix Metallopeptidase 1; COL1A1, collagen type I A1.

The transformation of melanocytes into cutaneous melanomas largely depends on the effects of solar UVR; however, the exact underlying mechanism remains unclear. Sha *et al* (82) reported that most UV-responsive miRNAs, including miR-193b, miR-342-3p, miR186, miR-130a and miR-146a, were downregulated in the melanocytes of a group of women with a history of melanoma compared with healthy controls. The UV miRNA gene regulatory network, which controls EMT and regulates immune evasion, was constructed based on the DIANA TarBase database (https://dianalab.e-ce.uth.gr/html/diana/web/index.php?r=tarbasev8). It was hypothesized that these pathways are activated by UVR, resulting in the downregulation of miRNAs only in melanocytes prone to melanoma. By analyzing the sequencing dataset, Chen *et al* (83) screened 218 genes and 104 miRNAs with abnormal expression under UVR. Among these, 29 upregulated and 28 downregulated miRNAs were found to be involved in the melanoma pathway. Furthermore, growth arrest and DNA damage inducible beta (GADD45B) was the only differentially expressed gene in the melanoma pathway, and miR-300 was the only differentially expressed miRNA that regulated GADD45B. Compared with normal melanocytes, miR-300 was significantly downregulated in melanoma cells and exosomes, which plays an important role in melanoma by inhibiting GADD45B expression. To screen for molecular biomarkers of UVB-induced skin damage, Qiang and Zhang (84) identified 16 upregulated genes based on the Gene Expression Omnibus database (https://www.ncbi.nlm.nih.gov/geo/). Using multiple online miRNA databases, it was proposed that MLANA-miR-573-MALAT1/NEAT1 and GPR143-miR-138-5p-MALAT1/ KCNQ1OT1 are potential RNA regulatory pathways for controlling the progression of UVB-induced skin diseases. Gene Ontology (GO) analysis revealed that these pathways were primarily related to melanin biosynthesis and metabolism.

Role of lncRNA in UV-induced pigmentation. After 24 h of UVB irradiation, the expression of lnc-GKN2-1:1 and ROS

levels increased significantly. The ROS scavenger (NAC) can reduce ROS generation and inhibit the upregulation of lnc-CD1D-2:1. Additionally, silencing lnc-CD1D-2:1 not only inhibited UVB-induced tyrosinase (TYR) mRNA expression and activation but also inhibited p38 phosphorylation. These results suggested that lncRNAs are involved in UVB-induced melanogenesis and that the expression of several lncRNAs depends on ROS generation (85). Taurine upregulated gene 1 (TUG1) is a significant member of the lncRNA family that is essential for the regulation of cell growth and stress response (86). After UVB irradiation, upregulation of TUG1, TYR and tyrosine-related protein 1/2 (TYRP1/2) in Pig1 melanocytes was reported by Fu *et al* (87). Interestingly, the inhibition of TUG1 resulted in a significant increase in the expression of TYR, TYRP1 and TYRP2 and decreased ERK phosphorylation. In addition, TUG1 silencing was revealed to suppress the expression of IL-6 and TNF-α in HaCaT cells. Collectively, TUG1 negatively regulates melanogenesis in melanocytes through the ERK pathway and silencing its expression can inhibit UVB-induced inflammatory responses in keratinocytes.

The lncRNA H19 has been reported to be involved in melanogenesis (88); however, whether UVB irradiation can alter H19 expression is unclear. Pei *et al* (89) revealed that the expression of H19 in keratinocytes decreased after UVB irradiation, and the levels of pro-opiomelanocortin (POMC), α-MSH and p53 were upregulated in the cells. In addition, H19 siRNAs significantly increased the expression of POMC, α-MSH and p53. After keratinocyte supernatants transfected with H19 siRNA were co-cultured with Pig1 cells, upregulation of MITF, TYR and Rab27A was detected in Pig1 cells. Collectively, UVB-inhibited H19 may promote α-MSH secretion by p53 in keratinocytes, and then regulate melanogenesis of melanocytes through paracrine effects. Another study (90) revealed that the expression of lncRNA UCA1 was negatively correlated with melanin content in melanocytes and pigmented nevi. Enhanced UCA1 expression downregulates melanin content and melanogenesis-related gene expression in UVB-induced melanocytes, whereas UCA1 knockdown has the opposite effect. High-throughput sequencing revealed that MITF and its upstream transcription factor CREB were negatively regulated by UCA1, which may serve as a potential therapeutic target for UV-related pigmented skin diseases.

Role of circRNA in UV-induced pigmentation. ciRS-7 is the most well-known circRNA and has important functions in the regulation of tumors, diabetes, cardiovascular diseases and neurodegenerative diseases (91). Ouyang *et al* (92) first demonstrated that UVB-induced ciRS-7 activates melanogenesis through paracrine effects. UVB irradiation promoted the expression of ciRS-7 in HaCaT cells and HDFs. After inhibiting the expression of ciRS-7 in HaCaT cells and HDFs, the supernatant of these cultured cells suppressed melanogenesis in melanocytes. Further analyses revealed that the phosphorylation of STAT3 and AKT significantly decreased in both cell lines following ciRS-7 inhibition, whereas miR-7 expression increased. In addition, the expression and secretion of fibroblast growth factor 2 (FGF2) were significantly downregulated in HDFs. Overexpression of miR-7 in HaCaT cells and HDFs significantly inhibits FGF2 expression. These results indicated that UVB-induced ciRS-7 triggered melanogenesis in MCs by regulating the miR-7/STAT3 and AKT/FGF2 paracrine axes in keratinocytes and fibroblasts (Table III).

6. Role of ncRNAs in UV-induced skin cancer

Role of miRNAs in UV-induced skin cancer. Cutaneous squamous cell carcinoma (cSCC) is the second most common malignancy worldwide, and UV damage is the most dangerous causative factor (93). UVC irradiation caused an increase in miR-125b expression in a biphasic manner and nuclear-cytoplasmic translocation of HuR. Binding of HuR to the p53 mRNA 3'UTR caused the dissociation of p53 mRNA from the RNA-induced silencing complex (RISC), thereby inhibiting miR-125b-mediated translation repression of p53. HuR prevents the oncogenic effects of miR-125b by reversing the decreased apoptosis and increased cell proliferation caused by miR-125b overexpression. The antagonism between miR-125b and HuR may regulate p53 gene expression at the post-transcriptional level, thereby regulating the cellular response to genotoxic stress induced by UVR (94). Wang *et al* (95) reported that the expression of miR-27a was significantly decreased in cSCC cells and tissues after UVB irradiation, and that miR-27a could inhibit the proliferation and invasion of cSCC cells. Mechanistically, miR-27a directly targets EGFR to inhibit its expression and suppresses the phosphorylation of EGFR and NF-κB to inhibit tumor growth and metastasis. Chitsazzadeh *et al* (96) revealed that miR-181a can promote tumorigenesis by targeting TGFβR3, an understudied component of TGFβ signaling. miR-181a and TGFβR3 were up-regulated and down-regulated in cSCC, respectively. miR-181a overexpression and TGFβR3 knockdown significantly inhibited UV-induced apoptosis and enhanced anchorage-independent survival in HaCaT and NHEK cells. The inhibition of miR-181a compromised tumor growth *in vivo*, further highlighting the importance of miRNA regulation in cSCC.

Moreover, miRNAs exert inhibitory effects on UV-induced skin cancers. TAp63, a member of the p53 family, is a potent tumor and metastasis suppressor (97). Davis *et al* (98) discovered that TAp63-/- mice show increased sensitivity to UV-induced cSCC, accompanied by decreased expression of miR-30c-2 and miR-497. Reintroduction of these miRNAs suppressed tumor growth in cSCC cell lines. Proteomic analysis revealed downregulation of cell cycle progression- and mitosis-associated proteins in cells expressing either miRNA. Furthermore, the miR-30c-2 and miR-497 miRNA mimics effectively inhibited cSCC growth *in vivo*. Harada *et al* (99) revealed that miR-124 was the most upregulated miRNA in senescent facial skin compared with young facial skin using a PCR array. Transfection of miR-124 mimic in normal human epidermal keratinocytes (NHEKs) resulted in a significant increase in the number of senescence-associated β-galactosidase (SA-β-gal)-positive NHEKs. Interestingly, miR-124 expression increased in a dose-dependent manner in UVB-irradiated NHEKs compared with that in controls, suggesting that miR-124 levels may increase as a result of UV irradiation rather than intrinsic aging. Compared with NHEKs, the expression of miR-124 was significantly decreased in A431 cells, a cSCC cell line. Overexpression of miR-124 in A431

Table III. Role of ncRNAs in UV-induced pigmentation.

ncRNAs	UV type	Dose	Alteration	Cells/Tissues	Targeted molecules	Mechanisms and pathways	(Refs.)
miR-148a	UVB	50 and 200 mJ/cm^2	↑	MNT-1	MITF	Regulating MITF oscillation	(74)
miR-340	UVB	100 mJ/cm^2	↑	PIG1	RhoA	Promoting melanosomes transport	(75)
miR-340	UVB	100 mJ/cm^2	↑	PIG1	MITF	Inhibiting melanin synthesis	(19)
miR-21	UVA	Unknown	↑	A375.S2	α-MSH	Activating Akt and EGFR	(76)
miR-203	UVB	30 mJ/cm^2	↑	black keratinocytes	Exosomes	Promoting pigmentation	(77)
miR-3196	UVB	30 mJ/cm^2	↑	Caucasian keratinocytes	Exosomes	Promoting pigmentation	(77)
miR-21	UVA	60 J/cm^2	↑	HPMs	TGF-β; IL-6; STAT3	Promoting proliferation and anti-apoptosis	(78)
miR-203a	UVB	11 mJ/cm^2	↑	HEKs	Cav1	Regulating exosomes	(79)
miR-300	UVB	70 mJ/cm^2	↓	A375	GADD45B	Regulating melanoma pathway	(83)
lncRNA lnc-CD1D-2:1	UVB	20 mJ/cm^2	↑	Primary melanocytes	TYR	Promoting melanogenesis	(85)
lncRNA TUG1	UVB	20 mJ/cm^2	↑	PIG1	TYR; TYRP1/2	Inhibiting melanogenesis by ERK	(87)
lncRNA H19	UVB	20 mJ/cm^2	↓	HaCaT	p53; α-MSH	Regulating melanogenesis	(88)
lncRNA UCA1	UVB	20 mJ/cm^2	↑	PIG1	MITF; CREB	Inhibiting melanogenesis	(90)
circRNA ciRS-7	UVB	60 mJ/cm^2	↑	HaCaT; HDFs	miR-7; FGF2; STAT3	Promoting melanogenesis	(92)

Nc, non-coding; UV, ultraviolet; miR, microRNA; lnc, long non-coding; circ, circular; MITF, melanocyte inducing transcription factor; α-MSH, proopiomelanocortin; RhoA, Ras homolog family member A; Cav1, caveolin 1; GADD45B, growth arrest and DNA damage inducible beta; TYR, tyrosinase; CREB, CAMP responsive element binding protein 1; FGF2, fibroblast growth factor 2.

cells significantly decreased the proportion of cancer cells. These results suggested that miR-124 expression increases owing to UVB-induced cellular senescence and decreases during tumorigenesis. The effect of miR-124 supplementation in cSCC cell lines suggests that senescence induction by miRNAs may be a novel therapeutic approach for SCC.

Role of lncRNA in UV-induced skin cancer. The mutation of a single p53 allele is an early event in skin cancer that enables keratinocytes to escape apoptosis and cell cycle arrest under continuous UVB irradiation (100). LincRNA-p21 is a lncRNA that is a transcriptional target of p53 and HIF-1α (101). Hall *et al* (102) found that UVB induces lincRNA-p21 transcription in mouse and human keratinocytes, primarily through a p53-dependent pathway. Knockdown of lincRNA-p21 suppressed UVB-induced apoptosis in mouse and human keratinocytes and had no effect on cell proliferation in UVB-irradiated or non-irradiated keratinocytes. Furthermore, mutation of a single p53 allele provides a pro-oncogenic function in the early stages of skin cancer by suppressing the UVB-induced expression of lincRNA-p21 and circumventing UVB-induced apoptosis. Kim *et al* (103) conducted a microarray analysis of lncRNA and mRNA expression levels in UVB-irradiated skin cells. GO analysis revealed that the expression of immune response-and cell membrane-related genes was upregulated under UVB irradiation, whereas the expression of cell-cell adhesion-related genes was downregulated. Furthermore, it was found that lncRNAs upregulated by UVB irradiation were related to transcriptional regulation, whereas downregulated lncRNAs were related to tumorigenesis. The aforementioned study lays the foundation for further studies on the expression patterns of lncRNAs that play a role in UV exposure and non-melanoma skin cancers. In addition to skin cancer, UVR-induced ncRNAs also play a role in other tumors. UV irradiation can effectively reduce the expression of miR-574-5p in HeLa cells and inhibit the migration of human cervical cancer cells (104). The expression of miR-9 was significantly increased in CNE2 cells (a nasopharyngeal carcinoma cell line) exposed to UV irradiation, and the inhibition of miR-9 expression promoted UV-induced DNA damage and apoptosis (105). Mechanistically, miR-9 reduced the sensitivity to UV radiation by increasing the level of glutathione in CNE2 cells (Table IV).

7. Role of ncRNAs in UV-induced ocular diseases

Role of miRNAs in UV-induced ocular diseases. Age-related cataract (ARC) is associated with DNA damage, and UVR causes oxidative damage in human lens epithelial cells (HLECs) (106). Dong *et al* (107) revealed that the expression level of miRNA let-7b in the anterior lens capsule of the ARC was higher than that in the normal anterior lens capsule, and

Table IV. Role of ncRNAs in UV-induced tumorigenesis.

ncRNAs	UV type	Dose	Alteration	Cells/Tissues	Targeted molecules	Mechanisms and pathways	(Refs.)
miR-125b	UVC	10 J/m^2	↑	MCF7	p53	Inhibiting apoptosis and increasing proliferation	(94)
miR-27a	UVB	30 and 300 mJ/cm^2	↓	HaCaT; Skin (BALB/C mice)	EGFR	Inhibiting tumor growth and metastasis	(95)
miR-574-5p	Unknown	Unknown	↓	HeLa	Unknown	Affecting cell proliferation in cervical cancer cells	(104)
miR-9	Unknown	Unknown	↑	CNE2	Glutathione	Increasing radiosensitivity in carcinoma nasopharyngeal	(105)
miR-124	UVB	5 and 10 mJ/cm^2	↓	A431	Unknown	Reducing the proportion of cancer cells	(99)
LincRNA-p21	UVB	10 mJ/cm^2	↑	Balb/MK2	p53	Promoting tumorigenesis by inhibiting apoptosis	(102)

Nc, non-coding; UV, ultraviolet; miR, microRNA.

that in LECs irradiated with UVB was higher than that in the control group. In addition, a leucine-rich repeat-containing G protein-coupled receptor 4 (Lgr4) was revealed to be a direct target of let-7b, which can regulate LECs apoptosis by directly targeting Lgr4. Cao *et al* (108) demonstrated that let-7c-5p contributes crucially to the inhibition of autophagic degradation in the ARC by targeting excision repair 6, chromatin remodelling factor. Sun *et al* (109) reported that UVR-induced cytotoxicity and apoptosis in HLECs could be enhanced by miR-4532 overexpression, NFE2 like BZIP transcription factor 2 (Nrf2) deletion, or SIRT6 shRNA. By contrast, miR-4532 inhibition or ectopic SIRT6 overexpression alleviated UVB-induced oxidative damage in HLECs. Significantly, miR-4532 overexpression or inhibition was ineffective in SIRT6-KO or Nrf2-KO HLECs. These results indicated that miR-4532 inhibition protects HLECs from UVR-induced oxidative damage by activating the SIRT6-Nrf2 pathway. Kang *et al* (110) revealed that miR-125a-3p expression is upregulated in ARC tissues and LECs treated with UVB. Downregulation of miR-125a-3p in LECs significantly reduced apoptosis and increased survival of UVB-irradiated LECs. The luciferase reporter gene detection demonstrated that miR-125a-3p may inhibit the translation of transmembrane Bax inhibitor motif containing 4 (TMBIM4) protein by binding to the 3'UTR of TMBIM4 mRNA, and overexpression of miR-125a-3p reduced the expression of TMBIM4. UVB irradiation enhanced LECs exosome secretion and high expression of miR-125a-3p. After UVB-exos treatment, cell viability significantly decreased, and apoptosis increased. miR-125a-3p regulates apoptosis by inhibiting TMBIM4 in LECs under oxidative damage conditions, providing a new approach for the treatment of cataracts.

Long-term exposure to UV radiation increases the retinal absorption of UVB and may lead to age-related eye diseases. Cheng *et al* (111) revealed that UV-induced ROS production and cell death are significantly attenuated in miR-141-expressing human retinal pigment epithelial cells (RPEs) and retinal ganglion cells (RGCs). Deletion of miR-141 resulted in the upregulation of kelch like ECH associated protein 1 (Keap1) and degradation of Nrf2, which aggravated the UV-induced death of RPEs cells and RGCs. Notably, Nrf2 knockdown almost completely abolished the cytoprotective effects of miR-141 against UVR in RPEs cells. These findings suggested that miR-141 activates Nrf2 signaling by targeting Keap1, thereby protecting RPEs cells and RGCs from UV radiation. RPEs degeneration is an important event in UVB-mediated age-related macular degeneration (AMD) (112). Yan *et al* (18) revealed that UVB significantly increased the levels of miR-340, among eight candidate miRNAs that may regulate the expression of protein phosphatase 1 regulatory subunit 13 like (iASPP), an inhibitory regulator of apoptosis. It was also confirmed that miR-340 repressed iASPP expression by directly binding to its 3'UTR. Collectively, UVB irradiation inhibits iASPP expression through inducing miR-340 expression, thereby promoting RPEs apoptosis and suppressing cell viability by affecting the expression of p21, p53, and caspase-3.

The corneal endothelium is critical for maintaining corneal transparency, and existing evidence has highlighted the effects of UVR on corneal epithelial cell (CEC) damage (113); however, the role of miRNAs is unclear. In a study by Yang *et al* (114), miR-129-5p had been shown to directly targeted EGFR. The inhibition of miR-129-5p can reduce the expression levels of various inflammatory factors in CECs and improve their antioxidant capacities. In addition, miR-129-5p inhibition arrested the cells in the S and G2 phases and reduced apoptosis. Therefore, inhibition of miR-129-5p may aid in the repair of CEC damage caused by UVR. Fu *et al* (115) revealed that UVB irradiation reduced the viability and proliferation of CECs and increased their apoptosis and autophagy. Compared with the CECs in the control group, the expression of miR-205-3p was significantly decreased in the UVB-treated group. Additionally, miR-205-3p overexpression increased the viability and proliferation of UVB-irradiated CECs and weakened apoptosis and autophagy. Further analyses revealed

that miR-205-3p protected CECs from UVB damage by inhibiting autophagy via targeting TLR4. These findings provide novel insights into the molecular mechanisms underlying UV-induced corneal damage.

Role of lncRNA in UV-induced ocular diseases. As miRNA sponges, lncRNA plays an important regulatory role in UV-induced visual impairment. Li *et al* (116) reported that TUG1 expression in the anterior lens capsule of the ARC was significantly higher than that in the normal anterior lens capsule, whereas the expression level of miR-421 was decreased. Apoptosis-related proteins were abnormally expressed in the anterior lens capsule of ARC tissue, such as caspase-3, Bax and Bcl-2. In addition, the apoptosis rate and expression of TUG1 and caspase-3 in UVB-irradiated SAR01/04 cells were significantly higher than those in control cells. These results suggested that TUG1 promotes UVB-induced apoptosis through the miR-421/caspase-3 axis in LECs, providing new insights into the pathogenesis of cataracts. Shen and Zhou (117) revealed that inhibition of TUG1 expression can protect HLECs from oxidative stress-induced apoptosis by upregulating miR-196a-5p expression in the ARC. Cheng *et al* (118) observed that lncRNA H19 and thymine DNA glycosylase (TDG) were highly expressed in early ARC tissues and HLECs exposed to UVB irradiation, whereas miR-29a was downregulated. Knockdown of lncRNA H19 reduced cell viability and proliferation, and promoted oxidative damage and apoptosis in HLECs, whereas overexpression of lncRNA H19 had the opposite effects. Mechanistically, miR-29a inhibited its TDG expression by binding to its 3'UTR. LncRNA H19 sponges miR-29a as a ceRNA and upregulates TDG expression by inhibiting miR-29a.

AMD can cause irreversible vision loss (119). ARPE-19 cells (AMD cell model) were treated with the multi-module stressful conditions described by Yu *et al* (120), including tert-butylhydroperoxide (t-BuOOH) and UVB irradiation. The results revealed that multimodule stress conditions induced ARPE-19 cell apoptosis and lncRNA PWRN2 upregulation and that PWRN2 overexpression aggravated t-BuOOH-induced ARPE-19 cell injury. Progressive loss of CECs during aging has been implicated in the development of Fuchs' endothelial corneal dystrophy (FECD), which is a primary cause of corneal-related vision loss (121). Unsupervised cluster analysis by Wang *et al* (122) revealed that NEAT1, an lncRNA, was most highly expressed in the C0-endothelial subpopulation but was significantly downregulated in FECD. Consistent with the human corneas, the UVA-induced mouse FECD model validated the loss of NEAT1 expression, and the loss of NEAT1 function reproduced the exacerbated FECD phenotype. Conversely, corneal protection from UVA-induced FECD was achieved using a CRISPR-activated adenoviral delivery system. This finding suggests that targeting lncRNA NEAT1 may provide an attractive approach for the treatment of FECD.

Role of circRNA in UV-induced ocular diseases. UVB irradiation induces age-related cortical cataracts (ARCC) by triggering DNA double-strand breaks (DDSBs) and senescence in LECs (123). DDSB-induced irreversible cell cycle arrest depends on ATM overactivation. Liu *et al* (124) revealed that the expression of circMRE11A-013 (circMRE11A) is upregulated in the LECs of ARCC and UVB-irradiated SRA01/04 cells. CircMRE11A knockdown in SRA01/04 cells improved cell survival and cell cycle progression, whereas circMRE11A overexpression revealed the opposite trend. Mechanistically, circMRE11A enhanced the overactivation of ATM and initiated the ATM/p53/p21 signaling pathway by binding to UBX domain-containing protein 1, resulting in cell cycle arrest and senescence of LECs. After rAAV-2 virions of circMRE11A were injected into the vitreous cavity of mice, LEC aging and lens opacity were observed 8 weeks later. The aforementioned study revealed a previously unidentified role for circMRE11A in inhibiting the cell cycle of LECs and accelerating ARCC formation. However, another circRNA, circEPB41, has a protective function in ARC (125). Compared with the control group, the expression of circEPB41 and 3'(2'), 5'-bisphosphate nucleotidase 1 (BPNT1) were downregulated in anterior lens capsule of ARC tissues and UVB-irradiated SRA01/04 cells. Overexpression of circEPB41 ameliorates the effects of UVB irradiation on the proliferation and apoptosis of SRA01/04 cells. Mechanistically, miR-24-3p, a target miRNA of circEPB41, attenuated circEPB41 introduction-mediated proliferation and apoptosis of UVB-irradiated SRA01/04 cells. Mechanistically, miR-24-3p regulates the UVB-induced effects by targeting BPNT1, and circEPB41 stimulates BPNT1 production via miR-24-3p. In conclusion, circEPB41 overexpression improved the UVB-induced apoptosis of LECs through the miR-24-3p/BPNT1 pathway, which offers a potential target for the treatment of UV-induced ARC (Table V).

8. Application of biological therapy targeting ncRNA in UV-induced radiation effect

At present, there is a limited number of studies regarding targeting ncRNAs for UVR-induced diseases. Moreover, most of these studies are in the basic research stage and have not been put into clinical practice. Several studies have revealed that miRNA-based strategies can be used to combat UVR-induced photodamage. Kansal *et al* (126) reported that regular intake of green tea polyphenols (GTPs) suppressed UVB radiation-induced skin cancer through miR-29-mediated epigenetic modification. Administration of GTPs blocked UVB-induced depletion of miR-29s and prevented tumor growth by reducing DNA hypermethylation and activating tumor suppressors. Arctiin, a lignin compound purified from *Arctium lappa*, exerts multiple biological effects on mammalian cells, including antiviral and anti-inflammatory effects (127). Kim *et al* (128) identified the mechanism through which arctiin induces an increase in COL1A1 expression in HDFs. Downregulation of miRNA-378b by arctiin was associated with the expression of SIRT6 mRNA, a regulator of COL1A1 mRNA. Arctiin protected against the UVB-induced decrease in COL1A1 mRNA expression via the miR-378b/SIRT6 signaling pathway. Mycosporin-like amino acids have strong antioxidant activity, such as porphyra-334, which can prevent UV-induced ROS from damaging cells (129). Suh *et al* (130) revealed that porphyra-334-regulated miRNAs can target numerous genes involved in UV-mediated biological processes such as apoptosis, cell proliferation and translational elongation. Furthermore, the target genes of the upregulated miRNAs functionally promoted apoptosis and translational elongation,

Table V. Role of ncRNAs in UV-induced ocular diseases.

ncRNAs	UV type	Dose	Alteration	Cells/Tissues	Targeted molecules	Mechanisms and pathways	(Refs.)
miRNA let-7b	UVB	648 mJ/cm^2	↑	SRA01/04	Lgr4	Promoting apoptosis	(107)
miRNA let-7c-5p	UVB	27-243 mJ/cm^2	↑	SRA01/04	ERCC	Inhibiting autophagy	(108)
miR-4532	UVB	30 mJ/cm^2	↑	HLECs	SIRT6; Nrf2	Promoting apoptosis	(109)
miR-125a-3p	UVB	Unknown	↑	SRA01/04	TMBIM4	Promoting apoptosis	(110)
miR-141	UVB	30 mJ/cm^2	↑	ARPE-19	Keap1	Activating Nrf2 signaling	(111)
miR-340	UVB	30-90 mJ/cm^2	↑	ARPE-19	iASPP	Promoting apoptosis	(18)
miR-129-5p	UVB	100 mJ/cm^2	↑	CECs	EGFR	Promoting inflammation	(114)
miR-205-3p	UVB	216 mJ/cm^2	↓	CECs	TLR4	Inhibiting autophagy	(115)
lncRNA TUG1	UVB	648 mJ/cm^2	↑	SRA01/04	miR-421	Promoting apoptosis	(116)
lncRNA H19	UVB	Unknown	↑	SRA01/04	miR-29a	Inhibiting apoptosis	(118)
lncRNA PWRN2	UVB	0-2,000 mJ/cm^2	↑	ARPE-19	Unknown	Promoting apoptosis	(121)
lncRNA NEAT1	UVA	500-1,000 J/cm^2	↓	FECD mouse model	FECD	Aggravating FECD phenotype	(122)
circRNA circMRE11A	UVB	Unknown	↑	SRA01/04	UBXN1	Inducing cell cycle arrest	(124)
circRNA circEPB41	UVB	648 mJ/cm^2	↓	SRA01/04	miR-24-3p; BPNT1	Inhibiting apoptosis	(125)

Nc, non-coding; UV, ultraviolet; miR, microRNA; lnc, long non-coding; circ, circular; Lgr4, leucine-rich repeat containing G protein-coupled receptor 4; SIRT6, sirtuin 6; Nrf2, NFE2 like BZIP transcription factor 2; TMBIM4, transmembrane bax inhibitor motif containing 4; Keap1, kelch like ECH associated protein 1; iASPP, protein phosphatase 1 regulatory subunit 13 like; TLR4, Toll-like receptor 4; FECD, endothelial corneal dystrophy; UBXN1, UBX domain-containing protein 1; BPNT1, 3'(2'), 5'-bisphosphate nucleotidase 1.

whereas those of the downregulated miRNAs repressed these processes. Joo *et al* (131) revealed that *Trichosanthes kirilowii* extract (TKE) enhanced the repair of UVB-induced DNA damage at low doses in a comet assay. Western blotting and RT-qPCR confirmed that TKE significantly upregulated the expression of basic helix-loop-helix ARNT like 1, a core clock protein, and downregulated the expression of miR-142-3p. In addition, the inhibition of miR-142-3p was positively correlated with the repair activity of TKE. Kawano *et al* (132) revealed that the expression of miR-129-5p was significantly increased in senescent facial skin and UVB-irradiated human dermal microvascular endothelial cells (HDMECs), suggesting that miR-129-5p is involved in photoaging. Forced overexpression of miR-129-5p caused a significant reduction in HDMECs number, indicating that miR-129-5p-regulated genes are involved in apoptosis. Additionally, miR-129-5p expression was downregulated in endothelial cells following royal jelly treatment, which may prevent skin aging by maintaining cell numbers.

Topsentin is a bis (indolyl) imidazole alkaloid isolated from the marine sponge *Spongosorites genitrix*. Hwang *et al* (133) reported that topostin exerts photoprotective effects on UVB-irradiated HaCaT cells by inhibiting the expression of COX-2 and its upstream signaling pathways, AP-1 and MAPK. Mechanistically, topsentin could inhibit the expression of miR-4485 and its target gene TNF-α IP2. Lee *et al* (134) revealed that galangin attenuated the decrease in cell viability and skin aging induced by H2O2/UVB. This protective effect of galangin was related to the inhibition of miR-4535 expression, thereby promoting TGFβ/Smad collagen synthesis signaling and reducing epidermal hyperplasia, wrinkle formation and skin aging. Arda and Doğanlar (135) irradiated wheat grass with UVC to obtain specific SI-WmiRs and then applied the SI-WmiRs cocktail to UVB-irradiated HaCaT cells. The results revealed that SI-WmiRs transfection prevented lipid peroxidation and oxidative stress-related DNA damage by increasing the expression of antioxidant genes and promoting DNA repair. These findings demonstrated that cross-kingdom gene regulation may be an effective therapeutic strategy against UV-induced skin diseases.

The loss of melanocytes from the epidermis is due to decreased adhesion of melanocytes to the surrounding keratinocytes, which is a key step in the pathogenesis of vitiligo (136). Clinical studies have confirmed that UVB phototherapy can induce melanocyte migration to the lesion area in patients with vitiligo; however, little is known regarding the mechanism underlying melanocyte migration (137). Su *et al* (138) found that miR-9 was increased in human lesional vitiligo specimens, and adhesion molecules such as E-cadherin and β1 integrin were decreased. *In vitro*, an increase in IL-10 levels induced by UVB exposure significantly reduced miR-9 expression by inducing its methylation in HaCaT cells. Furthermore, miR-9 inhibited the migration of PIG1 cells to UVB-irradiated HaCaT cells by targeting E-cadherin and β1 integrin. These findings enhance the understanding of vitiligo pathogenesis and further demonstrate that UVB-mediated repair of skin lesions may be a useful therapeutic strategy for treating vitiligo. Another study revealed that the levels of p53 and MMP9 were significantly upregulated in melanocytes exposed to single or repeated UVB irradiation, whereas the

Table VI. Application of biological therapy targeting ncRNA in UV-induced radiation effect.

Targeted treatments	Mechanisms and consequences	(Refs.)
GTPs	GTPs blocked UVB-induced depletion of miR-29s and prevented tumor growth by reducing DNA hypermethylation and activating tumor suppressors.	(126)
Arctiin	Arctiin protected against UVB-induced decrease in COL1A1 mRNA expression in HDFs by miR-378b/SIRT6 signaling pathway.	(128)
Porphyra-334	Porphyra-334 protected cells from harmful UV radiation through comprehensively regulating gene expression patterns by miRNAs.	(130)
TKE	TKE enhanced the repair of UVB-induced DNA damage through regulating the expression of miR-142-3p and BMAL1.	(131)
Royal jelly	Royal jelly prevented skin aging by downregulating miR-129-5p expression in UVB-irradiated HDMECs.	(132)
Topsentin	Topsentin had a photoprotective effect on HaCaT cells under UVB irradiation by inhibiting the expression of miR-4485 and its target gene TNF-α IP2.	(133)
Galangin	Galangin attenuated UVB-induced skin aging by the inhibition of miR-4535 expression, thereby promoting TGFβ/Smad collagen synthesis signaling.	(134)
SI-WmiR	SI-WmiRs transfection prevented lipid peroxidation and oxidative stress-related DNA damage by increasing the gene expression of antioxidant and DNA repair and inhibited the apoptosis of HaCaT cells under UV stress.	(135)
UVB phototherapy	UVB phototherapy reduced miR-9 expression through inducing its methylation, thereby inhibiting the migration of PIG1 cells to HaCaT cells by targeting E-cadherin and β1 integrin during vitiligo re-pigmentation.	(138)
Rh3	Rh3 protected retinal cells from UV damage by inducing miR-141 expression and down-regulating its target gene Keap1, thereby activating Nrf2 pathway.	(141)
ASC-exo	ASC-exo attenuated apoptosis in HLECs through reversing the inhibition of miR-10a-5p and high expression of CRTAC1 by UVB radiation.	(143)

Nc, non-coding; UV, ultraviolet; COL1A1, collagen type I A1; BMAL1, basic helix-loop-helix arnt like 1; PIG1, galectin 7; Rh3, Ginsenoside Rh3; Keap1, kelch like ECH associated protein 1; Nrf2, NFE2 like BZIP transcription factor 2; CRTAC1, cartilage acidic protein 1.

expression of TRPM1 and miR-211 was significantly downregulated (139). Notably, p53 overexpression and miR-211 upregulation alter the migratory capacity of melanocytes. These results suggested that melanocyte migration is regulated by the p53-TRPM1/miR-211-MMP9 axis and that activation of this axis by UVB phototherapy may be an attractive therapeutic target for improving re-pigmentation in patients with vitiligo.

The potential cytoprotective and anti-inflammatory effects of Ginsenoside Rh3 (Rh3) have been studied (140); however, its therapeutic effect on UV-induced retinal cell damage has not been investigated. Tang *et al* (141) reported that Rh3 pretreatment suppresses UV-induced ROS production and subsequent apoptotic/non-apoptotic cell death in cultured human RPEs and RGCs. Rh3 induced the activation of Nrf2 in retinal cells, and Nrf2 knockdown nearly abolished the Rh3-induced protection of retinal cells against UV radiation. Mechanistically, Rh3 could induce the expression of miR-141, resulting in the downregulation of its target gene, Keap1, in the RPEs and RGCs. Cartilage acidic protein 1 (CRTAC1) encodes a protein containing Ca^{2+} binding domains, that can promote UVB-induced apoptosis of HLECs (142). Hong *et al* (143) reported that miR-10a-5p was expressed at low levels in cataract lesions, CRTAC1 was highly expressed, and miR-10a-5p negatively regulated CRTAC1. miR-10a-5p overexpression reduced UVB-induced ROS production, apoptosis, and Ca^{2+} levels in HLECs *in vitro*. Furthermore, exosomes secreted from adipose-derived stem cells (ASC-exo) reversed the inhibition of miR-10a-5p and high expression of CRTAC1 induced by UVB radiation. Through the regulation of miR-10a-5p and CRTAC1 expression, ASC-exo attenuated UVB-induced apoptosis in HLECs, providing new insights into the pathogenic mechanisms and treatment methods of cataracts (Table VI).

Most UVR-induced skin cancers can be nearly 100% cured through surgical resection, whereas those detected in late metastatic stages III and IV have 5-year survival rates that drop to 50 and 10-25%, respectively (144). However, effective treatment relies largely on an early diagnosis, which requires the identification of early biomarkers. Therefore, ncRNAs can be used for early diagnosis. However, the use of ncRNAs for early diagnosis of UVR-induced diseases still faces several challenges. For example, some studies (76,145) have shown conflicting results, and it remains uncertain whether ncRNA expression is high or low, and its early use as a diagnostic marker may mislead clinical practice. Even when the same research group used the same cell lines and the same intensity of UVA, the expression profiles of circRNAs were not identical (71,73). This deviation is considered to be due to the cell processing process, and it is recommended that this step be standardized. When

irradiating cells with UV, the UV irradiator should be used to monitor the UV intensity rather than calculating the irradiation time using only the power indicated by the UV lamp or the instructions. Owing to the use of a UV lamp, the radiation intensity gradually declines. Furthermore, from the current research, it appears that ncRNAs regulated by UVR are not closely related to each other, making it difficult to translate the therapeutic potential into clinical practice. However, these regulated ncRNAs can be studied in series, such as the lncRNA-miRNA signaling axis, to demonstrate their connections. In conclusion, the clinical application of ncRNAs as therapeutic targets still require significant research attention and further study. Due to the lack of clinical studies, further research is required to discover any side effects and other challenges associated with the clinical application of the various therapies.

9. Summary

In the present study, the role of ncRNAs in UV-induced radiation effects was reviewed based on the latest research, including cell death, photoaging, pigmentation, skin cancer in skin tissue and UV-induced visual impairment. Previous studies have revealed that UVR can regulate the expression of a variety of ncRNAs and that this effect may be wavelength-specific. Irradiated cells exhibit differential miRNA or lncRNA responses to UVA and UVB, indicating that selective modulation of signal transduction pathways occurs in response to different UV energies. In addition, the effect of UVR on miRNA expression also depends on the cell line used and the quality of UV radiation; some studies have suggested that this effect is related to the time of cell irradiation. The mechanism of action of ncRNAs in the effects of UV-induced radiation is complex. For example, miRNAs cannot only promote the apoptosis of irradiated cells but also inhibit it. The same miRNAs play different regulatory roles in different cell lines and under different irradiation conditions. The photoprotective effects of some targeted drugs or molecules were revealed to be related to alterations in the expression of specific ncRNAs. The downstream target proteins of these ncRNAs can act in anti-apoptotic and anti-inflammatory pathways through a variety of mechanisms, and their final effect is to promote cell survival. ncRNAs may be part of the innate response mechanism of cells to UVR damage. Therefore, therapeutic strategies targeting ncRNAs can be useful in combating UVR-induced photodamage.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Nature Science Foundation of Heilongjiang (grant no. LH2020H137).

Availability of data and materials

Not applicable.

Authors' contributions

HG conceived and designed the study. CZ and LS conducted literature search. LD collected and analyzed the data. XL wrote the first draft of the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Trucco LD, Mundra PA, Hogan K, Garcia-Martinez P, Viros A, Mandal AK, Macagno N, Gaudy-Marqueste C, Allan D, Baenke F, *et al*: Ultraviolet radiation-induced DNA damage is prognostic for outcome in melanoma. Nat Med 25: 221-224, 2019.
2. Bernard JJ, Gallo RL and Krutmann J: Photoimmunology: How ultraviolet radiation affects the immune system. Nat Rev Immunol 19: 688-701, 2019.
3. Voelker R: UV-C disinfecting device poses radiation risk. JAMA 326: 1667, 2021.
4. Nunomura CY and Sousa SJFE: Ultraviolet radiation and the human eye. Arq Bras Oftalmol: Sep 23, 2022 (Epub ahead of print).
5. Ortiz-Rodríguez LA, Reichardt C, Hoehn SJ, Jockusch S and Crespo-Hernández CE: Detection of the thietane precursor in the UVA formation of the DNA 6-4 photoadduct. Nat Commun 11: 3599, 2020.
6. Shaw A and Gullerova M: Home and away: The role of non-coding RNA in intracellular and intercellular DNA damage response. Genes (Basel) 12: 1475, 2021.
7. Ali SA, Peffers MJ, Ormseth MJ, Jurisica I and Kapoor M: The non-coding RNA interactome in joint health and disease. Nat Rev Rheumatol 17: 692-705, 2021.
8. Seal RL, Chen LL, Griffiths-Jones S, Lowe TM, Mathews MB, O'Reilly D, Pierce AJ, Stadler PF, Ulitsky I, Wolin SL and Bruford EA: A guide to naming human non-coding RNA genes. EMBO J 39: e103777, 2020.
9. Bustamante M, Hernandez-Ferrer C, Tewari A, Sarria Y, Harrison GI, Puigdecanet E, Nonell L, Kang W, Friedländer MR, Estivill X, *et al*: Dose and time effects of solar-simulated ultraviolet radiation on the in vivo human skin transcriptome. Br J Dermatol 182: 1458-1468, 2020.
10. Si C, Wang J, Ma W, Hua H, Zhang M, Qian W, Zhou B and Luo D: Circular RNA expression profile in human fibroblast premature senescence after repeated ultraviolet B irradiations revealed by microarray. J Cell Physiol 234: 18156-18168, 2019.
11. Brahmbhatt HD, Gupta R, Gupta A, Rastogi S, Misri R, Mobeen A, Ghosh A, Kothari P, Sitaniya S, Scaria V and Singh A: The long noncoding RNA MALAT1 suppresses miR-211 to confer protection from ultraviolet-mediated DNA damage in vitiligo epidermis by upregulating sirtuin 1. Br J Dermatol 184: 1132-1142, 2021.
12. Devany E, Park JY, Murphy MR, Zakusilo G, Baquero J, Zhang X, Hoque M, Tian B and Kleiman FE: Intronic cleavage and polyadenylation regulates gene expression during DNA damage response through U1 snRNA. Cell Discov 2: 16013, 2016.
13. Huo CY, Chang ML, Cheng H, Ma TT, Fu Y, Wang Y, Wang YY, Kan YC and Li DD: Small nucleolar RNA of silkworm can translocate from the nucleolus to the cytoplasm under abiotic stress. Cell Biol Int 45: 1091-1097, 2021.

14. Fang Y, Liu Y, Yan Y, Shen Y, Li Z, Li X, Zhang Y, Xue Z, Peng C, Chen X, *et al*: Differential expression profiles and function predictions for tRFs & tiRNAs in skin injury induced by ultraviolet irradiation. Front Cell Dev Biol 9: 707572, 2021.
15. Kraemer A, Chen I, Henning S, Faust A, Volkmer B, Atkinson MJ, Moertl S and Greinert R: UVA and UVB irradiation differentially regulate microRNA expression in human primary keratinocytes. PLoS One 8: e83392, 2013.
16. Zhang J, Zhou B, Xu Y, Chen X, Liu J, Gozali M, Wu D, Yin ZQ and Luo D: MiR-23a-depressed autophagy is a participant in PUVA- and UVB-induced premature senescence. Oncotarget 7: 37420-37435, 2016.
17. Yo K and Rünger TM: UVA and UVB induce different sets of long noncoding RNAs. J Invest Dermatol 137: 769-772, 2017.
18. Yan J, Qin Y, Yu J, Peng Q and Chen X: MiR-340/iASPP axis affects UVB-mediated retinal pigment epithelium (RPE) cell damage. J Photochem Photobiol B 186: 9-16, 2018.
19. Yang Y, Wei X, Bai J, Huang M, Hao T, Hao Y, Wang Y and Li C: MicroRNA-340 is involved in ultraviolet B-induced pigmentation by regulating the MITF/TYRP1 axis. J Int Med Res 48: 300060520971510, 2020.
20. Chen IP, Bender M, Spassova I, Henning S, Kubat L, Fan K, Degenhardt S, Mhamdi-Ghodbani M, Sriram A, Volkmer B, *et al*: UV-type specific alteration of miRNA expression and its association with tumor progression and metastasis in SCC cell lines. J Cancer Res Clin Oncol 146: 3215-3231, 2020.
21. Hart PH, Norval M, Byrne SN and Rhodes LE: Exposure to ultraviolet radiation in the modulation of human diseases. Annu Rev Pathol 14: 55-81, 2019.
22. Zheng Y, Xu Q, Peng Y, Gong Z, Chen H, Lai W and Maibach HI: Expression profiles of long noncoding RNA in UVA-induced human skin fibroblasts. Skin Pharmacol Physiol 30: 315-323, 2017.
23. Lin Y, Lin M, Liu Y, Zhang J, Lai W, Xu Q and Zheng Y: Predicting miRNA-lncRNA-mRNA network in ultraviolet A-induced human skin photoaging. J Cosmet Dermatol 20: 1875-1884, 2021.
24. Kwon SY, Kim IS, Bae JE, Kang JW, Cho YJ, Cho NS and Lee SW: Pathogen inactivation efficacy of mirasol PRT system and intercept blood system for non-leucoreduced platelet-rich plasma-derived platelets suspended in plasma. Vox Sang 107: 254-260, 2014.
25. Arnason NA, Johannson F, Landrö R, Hardarsson B, Irsch J, Gudmundsson S, Rolfsson O and Sigurjonsson OE: Pathogen inactivation with amotosalen plus UVA illumination minimally impacts microRNA expression in platelets during storage under standard blood banking conditions. Transfusion 59: 3727-3735, 2019.
26. Osman A, Hitzler WE, Meyer CU, Landry P, Corduan A, Laffont B, Boilard E, Hellstern P, Vamvakas EC and Provost P: Effects of pathogen reduction systems on platelet microRNAs, mRNAs, activation, and function. Platelets 26: 154-163, 2015.
27. Diallo I, Benmoussa A, Laugier J, Osman A, Hitzler WE and Provost P: Platelet pathogen reduction technologies alter the MicroRNA profile of platelet-derived microparticles. Front Cardiovasc Med 7: 31, 2020.
28. Ye H, Xu H, Qiao M, Guo R, Ji Y, Yu Y, Chen Y, Gai X, Li H, Liu Q and Zhuang Y: MicroRNA expression profiles analysis of apheresis platelets treated with vitamin B_2 and ultraviolet-B during storage. Transfus Apher Sci 60: 103079, 2021.
29. Ibbotson SH: A perspective on the use of NB-UVB phototherapy vs PUVA Photochemotherapy. Front Med (Lausanne) 5: 184, 2018.
30. Soonthornchai W, Tangtanatakul P, Meephansan J, Ruchusatsawat K, Reantragoon R, Hirankarn N and Wongpiyabovorn J: Down-regulation of miR-155 after treatment with narrow-band UVB and methotrexate associates with apoptosis of keratinocytes in psoriasis. Asian Pac J Allergy Immunol 39: 206-213, 2021.
31. Soonthornchai W, Tangtanatakul P, Meesilpavikkai K, Dalm V, Kueanjinda P and Wongpiyabovorn J: MicroRNA-378a-3p is overexpressed in psoriasis and modulates cell cycle arrest in keratinocytes via targeting BMP2 gene. Sci Rep 11: 14186, 2021.
32. Ele-Refaei AM and El-Esawy FM: Effect of narrow-band ultraviolet b phototherapy and methotrexate on MicroRNA (146a) levels in blood of psoriatic patients. Dermatol Res Pract 2015: 145769, 2015.
33. Parihar AS, Tembhre MK, Sharma VK, Gupta S, Chattopadhyay P and Deepak KK: Effect of narrowband ultraviolet B treatment on microRNA expression in active nonsegmental generalized vitiligo. Br J Dermatol 183: 167-169, 2020.
34. Xiang Y, Laurent B, Hsu CH, Nachtergaele S, Lu Z, Sheng W, Xu C, Chen H, Ouyang J, Wang S, *et al*: RNA m^6A methylation regulates the ultraviolet-induced DNA damage response. Nature 543: 573-576, 2017.
35. Williamson L, Saponaro M, Boeing S, East P, Mitter R, Kantidakis T, Kelly GP, Lobley A, Walker J, Spencer-Dene B, *et al*: UV irradiation induces a non-coding RNA that functionally opposes the protein encoded by the same gene. Cell 168: 843-855. e13, 2017.
36. Liu J, Wu Z, He J and Wang Y: Cellular fractionation reveals transcriptome responses of human fibroblasts to UV-C irradiation. Cell Death Dis 13: 177, 2022.
37. Xu D, Wang Y, Wang J, Qi F and Sun Y: The potential regulatory roles of lncRNAs in DNA damage response in human lymphocytes exposed to UVC irradiation. Biomed Res Int 2020: 8962635, 2020.
38. Fathi N, Rashidi G, Khodadadi A, Shahi S and Sharifi S: STAT3 and apoptosis challenges in cancer. Int J Biol Macromol 117: 993-1001, 2018.
39. Liao XH, Zheng L, He HP, Zheng DL, Wei ZQ, Wang N, Dong J, Ma WJ and Zhang TC: STAT3 regulated ATR via microRNA-383 to control DNA damage to affect apoptosis in A431 cells. Cell Signal 27: 2285-2295, 2015.
40. Chowdhari S and Saini N: hsa-miR-4516 mediated downregulation of STAT3/CDK6/UBE2N plays a role in PUVA induced apoptosis in keratinocytes. J Cell Physiol 229: 1630-1638, 2014.
41. Chowdhari S and Saini N: Gene expression profiling reveals the role of RIG1 like receptor signaling in p53 dependent apoptosis induced by PUVA in keratinocytes. Cell Signal 28: 25-33, 2016.
42. Zheng X, Chen L, Jin S, Xiong L, Chen H, Hu K, Fan X, Fan S and Li C: Ultraviolet B irradiation up-regulates MM1 and induces photoageing of the epidermis. Photodermatol Photoimmunol Photomed 37: 395-403, 2021.
43. Li Y, Challagundla KB, Sun X, Zhang Q and Dai M: MicroRNA-130a associates with ribosomal protein L11 to suppress c-Myc expression in response to UV irradiation. Oncotarget 6: 1101-1114, 2015.
44. Zhang T, Qian H, Hu C, Lu H, Li J, Wu Y and Li W: MiR-26a mediates ultraviolet B-induced apoptosis by targeting histone methyltransferase EZH2 depending on Myc expression. Cell Physiol Biochem 43: 1188-1197, 2017.
45. Degueurce G, D'Errico I, Pich C, Ibberson M, Schütz F, Montagner A, Sgandurra M, Mury L, Jafari P, Boda A, *et al*: Identification of a novel PPARβ/δ/miR-21-3p axis in UV-induced skin inflammation. EMBO Mol Med 8: 919-936, 2016.
46. Ni N, Ma W, Tao Y, Liu J, Hua H, Cheng J, Wang J, Zhou B and Luo D: Exosomal MiR-769-5p exacerbates ultraviolet-induced bystander effect by targeting TGFBR1. Front Physiol 11: 603081, 2020.
47. Jiang SB, Lu YS, Liu T, Li LM, Wang HX, Wu Y, Gao XH and Chen HD: UVA influenced the SIRT1-miR-27a-5p-SMAD2-MMP1/COL1/BCL2 axis in human skin primary fibroblasts. J Cell Mol Med 24: 10027-10041, 2020.
48. Yang L, Hu Z, Jin Y, Huang N and Xu S: MiR-4497 mediates oxidative stress and inflammatory injury in keratinocytes induced by ultraviolet B radiation through regulating NF-κB expression. Ital J Dermatol Venerol 157: 84-91, 2022.
49. Yu B, Dong H, Zang Y, Jiang S, Luan H and Zhang Y: MicroRNA-139-5p alleviates UVB-induced injuries by regulating TLR4 in si-IL-6-treated keratinocyte cells. Int J Clin Exp Pathol 10: 9293-9301, 2017.
50. Zhang Y, Yang C, Yang S and Guo Z: MiRNA-27a decreases ultraviolet B irradiation-induced cell damage. J Cell Biochem 121: 1032-1038, 2020.
51. Zhang C, Xie X, Yuan Y, Wang Y, Zhou M, Li X and Zhen P: MiR-664 protects against UVB radiation-induced HaCaT cell damage via downregulating ARMC8. Dose Response 18: 1559325820929234, 2020.
52. Tu Y, Wu W, Guo Y, Lu F, Xu D, Li X, Zhao Y and He L: Upregulation of hsa-miR-31-3p induced by ultraviolet affects keratinocytes permeability barrier by targeting CLDN1. Biochem Biophys Res Commun 532: 626-632, 2020.
53. Tu Y, Wu W, Guo Y, Lu F, Li X, Xu D, Zou D, Tu Y, Chai Y and He L: Up-regulation of hsa-miR-221-3p induced by UVB affects proliferation and apoptosis of keratinocytes via Bcl-xL/Bax pathway. Photodermatol Photoimmunol Photomed 37: 269-277, 2021.
54. Rünger TM and Yo K: The UVA-induced long non-coding RNA GS1-600G8.5 regulates the expression of IL-8. J Dermatol Sci 90: 363-366, 2018.

55. Zhang N, Zhong Z, Wang Y, Yang L, Wu F, Peng C, Huang W and He G: Competing endogenous network analysis identifies lncRNA Meg3 activates inflammatory damage in UVB induced murine skin lesion by sponging miR-93-5p/epiregulin axis. Aging (Albany NY) 11: 10664-10683, 2019.
56. Liang M and Hu K: Involvement of lncRNA-HOTTIP in the repair of ultraviolet light-induced DNA damage in spermatogenic cells. Mol Cells 42: 794-803, 2019.
57. Kunkeaw N, Lee YS, Im WR, Jang JJ, Song MJ, Yang B, Park JL, Kim SY, Ku Y, Kim Y, *et al*: Mechanism mediated by a noncoding RNA, nc886, in the cytotoxicity of a DNA-reactive compound. Proc Natl Acad Sci USA 116: 8289-8494, 2019.
58. Lee KS, Shin S, Cho E, Im WK, Jeon SH, Kim Y, Park D, Fréchet M, Chajra H and Jung E: nc886, a non-coding RNA, inhibits UVB-induced MMP-9 and COX-2 expression via the PKR pathway in human keratinocytes. Biochem Biophys Res Commun 512: 647-652, 2019.
59. Lee KS, Cho E, Weon JB, Park D, Fréchet M, Chajra H and Jung E: Inhibition of UVB-induced inflammation by laminaria japonica extract via regulation of nc886-PKR pathway. Nutrients 12: 1958, 2020.
60. Kim Y, Ji H, Cho E, Park NH, Hwang K, Park W, Lee KS, Park D and Jung E: nc886, a non-coding RNA, is a new biomarker and epigenetic mediator of cellular senescence in fibroblasts. Int J Mol Sci 22: 13673, 2021.
61. Lang A, Grether-Beck S, Singh M, Kuck F, Jakob S, Kefalas A, Altinoluk-Hambüchen S, Graffmann N, Schneider M, Lindecke A, *et al*: MicroRNA-15b regulates mitochondrial ROS production and the senescence-associated secretory phenotype through sirtuin 4/SIRT4. Aging (Albany NY) 8: 484-505, 2016.
62. Joo D, An S, Choi BG, Kim K, Choi YM, Ahn KJ, An IS and Cha HJ: MicroRNA-378b regulates α-1-type 1 collagen expression via sirtuin 6 interference. Mol Med Rep 16: 8520-8524, 2017.
63. Blackstone BN, Wilgus TA, Roy S, Wulff BC and Powell HM: Skin biomechanics and miRNA expression following chronic UVB irradiation. Adv Wound Care (New Rochelle) 9: 79-89, 2020.
64. Li G, Luna C and Gonzalez P: miR-183 inhibits UV-induced DNA damage repair in human trabecular meshwork cells by targeting of KIAA0101. Invest Ophthalmol Vis Sci 57: 2178-2186, 2016.
65. Ishihara Y, Tsuno S, Ping B, Ashizaki T, Nakashima M, Miura K, Miura Y, Yamashita T, Hasegawa J and Miura N: Hsa-miR-520d-5p promotes survival in human dermal fibroblasts exposed to a lethal dose of UV irradiation. NPJ Aging Mech Dis 2: 16029, 2016.
66. Zhang X, Hamblin MH and Yin K: The long noncoding RNA Malat1: Its physiological and pathophysiological functions. RNA Biol 14: 1705-1714, 2017.
67. Lei L, Zeng Q, Lu J, Ding S, Xia F, Kang J, Tan L, Gao L, Kang L, Cao K, *et al*: MALAT1 participates in ultraviolet B-induced photo-aging via regulation of the ERK/MAPK signaling pathway. Mol Med Rep 15: 3977-3982, 2017.
68. Hou W, Lin Y, Xu W, Chen H, Liu Y, Li C and Zheng Y: Identification and biological analysis of LncSPRY4-IT1-targeted functional proteins in photoaging skin. Photodermatol Photoimmunol Photomed 37: 530-538, 2021.
69. Li M, Li L, Zhang X, Yan Y and Wang B: LncRNA RP11-670E13.6 regulates cell cycle progression in UVB damaged human dermal fibroblasts. Photochem Photobiol 94: 589-597, 2018.
70. Li M, Li L, Zhang X, Zhao H, Wei M, Zhai W, Wang B and Yan Y: LncRNA RP11-670E13.6, interacted with hnRNPH, delays cellular senescence by sponging microRNA-663a in UVB damaged dermal fibroblasts. Aging (Albany NY) 11: 5992-6013, 2019.
71. Peng Y, Song X, Zheng Y, Wang X and Lai W: Circular RNA profiling reveals that circCOL3A1-859267 regulate type I collagen expression in photoaged human dermal fibroblasts. Biochem Biophys Res Commun 486: 277-284, 2017.
72. Peng Y, Song X, Zheng Y, Cheng H and Lai W: circ-COL3A1-859267 regulates type I collagen expression by sponging miR-29c in human dermal fibroblasts. Eur J Dermatol 28: 613-620, 2018.
73. Lin M, Zheng Y, Li Q, Liu Y, Xu Q, Li Y and Lai W: Circular RNA expression profiles significantly altered in UVA-irradiated human dermal fibroblasts. Exp Ther Med 20: 163, 2020.
74. Malcov-Brog H, Alpert A, Golan T, Parikh S, Nordlinger A, Netti F, Sheinboim D, Dror I, Thomas L, Cosson C, *et al*: UV-protection timer controls linkage between stress and pigmentation skin protection systems. Mol Cell 72: 444-456.e7, 2018.
75. Jian Q, An Q, Zhu D, Hui K, Liu Y, Chi S and Li C: MicroRNA 340 is involved in UVB-induced dendrite formation through the regulation of RhoA expression in melanocytes. Mol Cell Biol 34: 3407-3420, 2014.
76. Lin KY, Chen CM, Lu CY, Cheng CY and Wu YH: Regulation of miR-21 expression in human melanoma via UV-ray-induced melanin pigmentation. Environ Toxicol 32: 2064-2069, 2017.
77. Cicero AL, Delevoye C, Gilles-Marsens F, Loew D, Dingli F, Guéré C, André N, Vié K, van Niel G and Raposo G: Exosomes released by keratinocytes modulate melanocyte pigmentation. Nat Commun 6: 7506, 2015.
78. Wäster P, Eriksson I, Vainikka L and Öllinger K: Extracellular vesicles released by melanocytes after UVA irradiation promote intercellular signaling via miR21. Pigment Cell Melanoma Res 33: 542-555, 2020.
79. Zhang K, Yu L, Li FR, Li X, Wang Z, Zou X, Zhang C, Lv K, Zhou B, Mitragotri S and Chen M: Topical application of exosomes derived from human umbilical cord mesenchymal stem cells in combination with sponge spicules for treatment of photoaging. Int J Nanomedicine 15: 2859-2872, 2020.
80. Shen Z, Sun J, Shao J and Xu J: Ultraviolet B irradiation enhances the secretion of exosomes by human primary melanocytes and changes their exosomal miRNA profile. PLoS One 15: e237023, 2020.
81. Sha J, Arbesman J and Harter ML: Premature senescence in human melanocytes after exposure to solar UVR: An exosome and UV-miRNA connection. Pigment Cell Melanoma Res 33: 671-684, 2020.
82. Sha J, Gastman BR, Morris N, Mesinkovska NA, Baron ED, Cooper KD, McCormick T, Arbesman J and Harter ML: The response of microRNAs to solar UVR in skin-resident melanocytes differs between melanoma patients and healthy persons. PLoS One 11: e154915, 2016.
83. Chen L, Karisma VW, Liu H and Zhong L: MicroRNA-300: A transcellular mediator in exosome regulates melanoma progression. Front Oncol 9: 1005, 2019.
84. Qiang M and Zhang R: Identification of potential immune-related ceRNA regulatory network in UVB-irradiated human skin. Biotechnol Genet Eng Rev: 1-24, 2023 (Epub ahead of print).
85. Zeng Q, Wang Q, Chen X, Xia K, Tang J, Zhou X, Cheng Y, Chen Y, Huang L, Xiang H, *et al*: Analysis of lncRNAs expression in UVB-induced stress responses of melanocytes. J Dermatol Sci 81: 53-60, 2016.
86. Baliou S, Kyriakopoulos A, Spandidos D and Zoumpourlis V: Role of taurine, its haloamines and its lncRNA TUG1 in both inflammation and cancer progression. On the road to therapeutics? (Review). Int J Oncol 57: 631-664, 2020.
87. Fu C, Chen J, Lu J, Pei S, Hu S, Jiang L, Ding Y, Huang L, Xiang H, Huang J and Zeng Q: Downregulation of TUG1 promotes melanogenesis and UVB-induced melanogenesis. Exp Dermatol 28: 730-733, 2019.
88. Jin S, Chen L, Xu Z, Xing X, Zhang C and Xiang L: 585 nm light-emitting diodes inhibit melanogenesis through upregulating H19/miR-675 axis in LEDs-irradiated keratinocytes by paracrine effect. J Dermatol Sci 98: 102-108, 2020.
89. Pei S, Huang J, Chen J, Hu S, Lei L, Fu C, Jiang L, Ding Y, Leng Y, Huang L, *et al*: UVB-inhibited H19 activates melanogenesis by paracrine effects. Exp Dermatol 27: 1120-1125, 2018.
90. Pei S, Chen J, Lu J, Hu S, Jiang L, Lei L, Ouyang Y, Fu C, Ding Y, Li S, *et al*: The long noncoding RNA UCA1 negatively regulates melanogenesis in melanocytes. J Invest Dermatol 140: 152-163.e5, 2020.
91. Chen J, Yang J, Fei X, Wang X and Wang K: CircRNA ciRS-7: A novel oncogene in multiple cancers. Int J Biol Sci 17: 379-389, 2021.
92. Ouyang Y, Chen J, Jiang L, Li Y, Hu Y, Li S, Huang J and Zeng Q: UVB-induced ciRS-7 activates melanogenesis by paracrine effects. Dna Cell Biol 40: 523-531, 2021.
93. Tokez S, Wakkee M, Louwman M, Noels E, Nijsten T and Hollestein L: Assessment of cutaneous squamous cell carcinoma (cSCC) in situ incidence and the risk of developing invasive cSCC in patients with prior cSCC in situ vs the general population in the Netherlands, 1989-2017. JAMA Dermatol 156: 973-981, 2020.
94. Ahuja D, Goyal A and Ray PS: Interplay between RNA-binding protein HuR and microRNA-125b regulates p53 mRNA translation in response to genotoxic stress. RNA Biol 13: 1152-1165, 2016.
95. Wang Y, Deng X, Dai Y, Niu X and Zhou M: miR-27a downregulation promotes cutaneous squamous cell carcinoma progression via targeting EGFR. Front Oncol 9: 1565, 2020.

96. Chitsazzadeh V, Nguyen TN, de Mingo Pulido A, Bittencourt BB, Du L, Adelmann CH, Ortiz Rivera I, Nguyen KA, Guerra LD, Davis A, *et al*: miR-181a promotes multiple protumorigenic functions by targeting TGFβR3. J Invest Dermatol 142: 1956-1965.e2, 2022.
97. Gunaratne PH, Pan Y, Rao AK, Lin C, Hernandez Herrera A, Liang K, Rait AS, Venkatanarayan A, Benham AL, Rubab F, *et al*: Activating p53 family member TAp63: A novel therapeutic strategy for targeting p53-altered tumors. Cancer 125: 2409-2422, 2019.
98. Davis AJ, Tsinkevich M, Rodencal J, Abbas HA, Su XH, Gi YJ, Fang B, Rajapakshe K, Coarfa C, Gunaratne PH, *et al*: TAp63-regulated miRNAs suppress cutaneous squamous cell carcinoma through inhibition of a network of cell-cycle genes. Cancer Res 80: 2484-2497, 2020.
99. Harada M, Jinnin M, Wang Z, Hirano A, Tomizawa Y, Kira T, Igata T, Masuguchi S, Fukushima S and Ihn H: The expression of miR-124 increases in aged skin to cause cell senescence and it decreases in squamous cell carcinoma. Biosci Trends 10: 454-559, 2017.
100. Loureiro JB, Abrantes M, Oliveira PA and Saraiva L: P53 in skin cancer: From a master player to a privileged target for prevention and therapy. Biochim Biophys Acta Rev Cancer 1874: 188438, 2020.
101. Huarte M, Guttman M, Feldser D, Garber M, Koziol MJ, Kenzelmann-Broz D, Khalil AM, Zuk O, Amit I, Rabani M, *et al*: A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. Cell 142: 409-419, 2010.
102. Hall JR, Messenger ZJ, Tam HW, Phillips SL, Recio L and Smart RC: Long noncoding RNA lincRNA-p21 is the major mediator of UVB-induced and p53-dependent apoptosis in keratinocytes. Cell Death Dis 6: e1700, 2015.
103. Kim K, Kim H and Lee TR: Epidermal long non-coding RNAs are regulated by ultraviolet irradiation. Gene 637: 196-202, 2017.
104. Ma DL, Li JY, Liu YE, Liu CM, Li J, Lin GZ and Yan J: Influence of continuous intervention on growth and metastasis of human cervical cancer cells and expression of RNAmiR-574-5p. J Biol Regul Homeost Agents 30: 91-102, 2016.
105. Zheng CP, Han L, Hou WJ, Tang J, Wen YH, Fu R, Wang YJ and Wen WP: MicroRNA-9 suppresses the sensitivity of CNE2 cells to ultraviolet radiation. Mol Med Rep 12: 2367-2373, 2015.
106. Ang MJ and Afshari NA: Cataract and systemic disease: A review. Clin Exp Ophthalmol 49: 118-127, 2021.
107. Dong Y, Zheng Y, Xiao J, Zhu C and Zhao M: MicroRNA let-7b induces lens epithelial cell apoptosis by targeting leucine-rich repeat containing G protein-coupled receptor 4 (Lgr4) in age-related cataract. Exp Eye Res 147: 98-104, 2016.
108. Cao Y, Li P, Zhang G, Kang L, Zhou T, Wu J, Wang Y, Wang Y, Chen X and Guan H: MicroRNA Let-7c-5p-mediated regulation of ERCC6 Disrupts autophagic flux in age-related cataract via the binding to VCP. Curr Eye Res 46: 1353-1362, 2021.
109. Sun GL, Huang D, Li KR and Jiang Q: microRNA-4532 inhibition protects human lens epithelial cells from ultra-violet-induced oxidative injury via activating SIRT6-Nrf2 signaling. Biochem Biophys Res Commun 514: 777-784, 2019.
110. Kang L, Luo J, Li P, Zhang G, Wei M, Ji M and Guan H: miR-125a-3p regulates apoptosis by suppressing TMBIM4 in lens epithelial cells. Int Ophthalmol 43: 1261-1274, 2023.
111. Cheng LB, Li KR, Yi N, Li XM, Wang F, Xue B, Pan YS, Yao J, Jiang Q and Wu ZF: miRNA-141 attenuates UV-induced oxidative stress via activating Keap1-Nrf2 signaling in human retinal pigment epithelium cells and retinal ganglion cells. Oncotarget 8: 13186-13194, 2017.
112. Amari B, Merle BMJ, Korobelnik J, Delyfer M, Boniol M, Dore J, Helmer C, Delcourt C and Cougnard-Gregoire A: Lifetime ambient ultraviolet radiation exposure and incidence of age-related macular degeneration. Retina 44: 28-36, 2024.
113. Lombardo M, Pucci G, Barberi R and Lombardo G: Interaction of ultraviolet light with the cornea: Clinical implications for corneal crosslinking. J Cataract Refract Surg 41: 446-459, 2015.
114. Yang Y, Gong B, Wu ZZ, Shuai P, Li DF, Liu LL and Yu M: Inhibition of microRNA-129-5p expression ameliorates ultraviolet ray-induced corneal epithelial cell injury via upregulation of EGFR. J Cell Physiol 234: 11692-11707, 2019.
115. Fu JY, Yu XF, Wang HQ, Lan JW, Shao WQ and Huo YN: MiR-205-3p protects human corneal epithelial cells from ultraviolet damage by inhibiting autophagy via targeting TLR4/NF-κB signaling. Eur Rev Med Pharmacol Sci 24: 6494-6504, 2020.
116. Li G, Song H, Chen L, Yang W, Nan K and Lu P: TUG1 promotes lens epithelial cell apoptosis by regulating miR-421/caspase-3 axis in age-related cataract. Exp Cell Res 356: 20-27, 2017.
117. Shen Q and Zhou T: Knockdown of lncRNA TUG1 protects lens epithelial cells from oxidative stress-induced injury by regulating miR-196a-5p expression in age-related cataracts. Exp Ther Med 22: 1286, 2021.
118. Cheng T, Xu M, Qin B, Wu J, Tu Y, Kang L, Wang Y and Guan H: lncRNA H19 contributes to oxidative damage repair in the early age-related cataract by regulating miR-29a/TDG axis. J Cell Mol Med 23: 6131-6139, 2019.
119. Chakravarthy U and Peto T: Current perspective on age-related macular degeneration. JAMA 324: 794-795, 2020.
120. Yu X, Luo Y, Chen G, Liu H, Tian N, Zen X and Huang Y: Long non-coding RNA PWRN2 regulates cytotoxicity in an in vitro model of age-related macular degeneration. Biochem Biophys Res Commun 535: 39-46, 2021.
121. Ong Tone S, Kocaba V, Böhm M, Wylegala A, White TL and Jurkunas UV: Fuchs endothelial corneal dystrophy: The vicious cycle of Fuchs pathogenesis. Prog Retin Eye Res 80: 100863, 2021.
122. Wang Q, Dou S, Zhang B, Jiang H, Qi X, Duan H, Wang X, Dong C, Zhang BN, Xie L, *et al*: Heterogeneity of human corneal endothelium implicates lncRNA NEAT1 in Fuchs endothelial corneal dystrophy. Mol Ther Nucleic Acids 27: 880-893, 2022.
123. Wang Y, Li F, Zhang G, Kang L and Guan H: Ultraviolet-B induces ERCC6 repression in lens epithelium cells of age-related nuclear cataract through coordinated DNA hypermethylation and histone deacetylation. Clin Epigenetics 8: 62, 2016.
124. Liu J, Zhang J, Zhang G, Zhou T, Zou X, Guan H and Wang Y: CircMRE11A_013 binds to UBXN1 and integrates ATM activation enhancing lens epithelial cells senescence in age-related cataract. Aging (Albany NY) 13: 5383-5402, 2021.
125. Zhou C, Huang X, Li X and Xiong Y: Circular RNA erythrocyte membrane protein band 4.1 assuages ultraviolet irradiation-induced apoptosis of lens epithelial cells by stimulating 5'-bisphosphate nucleotidase 1 in a miR-24-3p-dependent manner. Bioengineered 12: 8953-8964, 2021.
126. Kansal V, Agarwal A, Harbour A, Farooqi H, Singh VK and Prasad R: Regular intake of green tea polyphenols suppresses the development of nonmelanoma skin cancer through miR-29-mediated epigenetic modifications. J Clin Med 11: 398, 2022.
127. Gao Q, Yang M and Zuo Z: Overview of the anti-inflammatory effects, pharmacokinetic properties and clinical efficacies of arctigenin and arctiin from *Arctium lappa* L. Acta Pharmacol Sin 39: 787-801, 2018.
128. Kim K, An S, Choi BG, Joo D, Choi YM, Ahn KJ, An IS and Cha HJ: Arctiin regulates collagen type 1α chain 1 mRNA expression in human dermal fibroblasts via the miR-378b-SIRT6 axis. Mol Med Rep 16: 9120-9124, 2017.
129. Wang K, Deng Y, He Y, Cao J, Zhang L, Qin L, Qu C, Li H and Miao J: Protective effect of mycosporine-like amino acids isolated from an antarctic diatom on UVB-induced skin damage. Int J Mol Sci 24: 15055, 2023.
130. Suh SS, Lee SG, Youn UJ, Han SJ, Kim IC and Kim S: Comprehensive expression profiling and functional network analysis of porphyra-334, one mycosporine-like amino acid (MAA), in human keratinocyte exposed with UV-radiation. Mar Drugs 15: 196, 2017.
131. Joo JH, Hong IK, Kim NK and Choi E: *Trichosanthes kirilowii* extract enhances repair of UVB radiation-induced DNA damage by regulating BMAL1 and miR-142-3p in human keratinocytes. Mol Med Rep 17: 877-883, 2018.
132. Kawano Y, Makino K, Jinnin M, Sawamura S, Shimada S, Fukushima S and Ihn H: Royal jelly regulates the proliferation of human dermal microvascular endothelial cells through the down-regulation of a photoaging-related microRNA. Drug Discov Ther 13: 268-273, 2019.
133. Hwang J, Kim D, Park JS, Park HJ, Shin J and Lee SK: Photoprotective activity of topsentin, A Bis(Indole) alkaloid from the marine sponge *Spongosorites genitrix*, by regulation of COX-2 and Mir-4485 expression in UVB-irradiated human keratinocyte cells. Mar Drugs 18: 87, 2020.
134. Lee JJ, Ng SC, Ni YT, Liu JS, Chen CJ, Padma VV, Huang CY and Kuo WW: Protective effects of galangin against H_2O_2/UVB-induced dermal fibroblast collagen degradation via hsa-microRNA-4535-mediated TGFβ/Smad signaling. Aging (Albany NY) 13: 25342-25364, 2021.
135. Arda H and Doğanlar O: Stress-induced miRNAs isolated from wheat have a unique therapeutic potential in ultraviolet-stressed human keratinocyte cells. Environ Sci Pollut Res Int 29: 17977-17996, 2022.

136. Singh M, Mansuri MS, Kadam A, Palit SP, Dwivedi M, Laddha NC and Begum R: Tumor necrosis factor-alpha affects melanocyte survival and melanin synthesis via multiple pathways in vitiligo. Cytokine 140: 155432, 2021.
137. Nguyen S, Chuah SY, Fontas E, Khemis A, Jhingan A, Thng STG and Passeron T: Atorvastatin in combination with narrowband UV-B in adult patients with active vitiligo: A randomized clinical trial. JAMA Dermatol 154: 725-726, 2018.
138. Su M, Yi H, He X, Luo L, Jiang S and Shi Y: miR-9 regulates melanocytes adhesion and migration during vitiligo repigmentation induced by UVB treatment. Exp Cell Res 384: 111615, 2019.
139. Su M, Miao F, Jiang S, Shi Y, Luo L, He X, Wan J, Xu S and Lei TC: Role of the p53-TRPM1/miR-211-MMP9 axis in UVB-induced human melanocyte migration and its potential in repigmentation. Int J Mol Med 45: 1017-1026, 2020.
140. Wu Y, Pi D, Zhou S, Yi Z, Dong Y, Wang W, Ye H, Chen Y, Zuo Q and Ouyang M: Ginsenoside Rh3 induces pyroptosis and ferroptosis through the Stat3/p53/NRF2 axis in colorectal cancer cells. Acta Biochim Biophys Sin (Shanghai) 55: 587-600, 2023.
141. Tang CZ, Li KR, Yu Q, Jiang Q, Yao J and Cao C: Activation of Nrf2 by Ginsenoside Rh3 protects retinal pigment epithelium cells and retinal ganglion cells from UV. Free Radic Biol Med 117: 238-246, 2018.
142. Sun Y, Rong X, Li D, Jiang Y, Lu Y and Ji Y: Down-regulation of CRTAC1 attenuates UVB-induced pyroptosis in HLECs through inhibiting ROS production. Biochem Biophys Res Commun 532: 159-165, 2020.
143. Hong Y, Sun Y, Rong X, Li D, Lu Y and Ji Y: Exosomes from adipose-derived stem cells attenuate UVB-induced apoptosis, ROS, and the Ca^{2+} level in HLEC cells. Exp Cell Res 396: 112321, 2020.
144. Mumford SL, Towler BP, Pashler AL, Gilleard O, Martin Y and Newbury SF: Circulating MicroRNA biomarkers in melanoma: Tools and challenges in personalised medicine. Biomolecules 8: 21, 2018.
145. Gu X, Nylander E, Coates PJ and Nylander K: Effect of narrow-band ultraviolet B phototherapy on p63 and microRNA (miR-21 and miR-125b) expression in psoriatic epidermis. Acta Derm Venereol 91: 392-397, 2011.