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Mitochondrial Sirtuins in Skin and Skin Cancers

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Abstract

Mammalian sirtuins (SIRTs 1-7), are a family of NAD+-dependent deacetylases with distinct subcellular localization and biological functions that regulate various important cellular processes. Among these, SIRTs −3, −4, and −5 are located in the mitochondria and have been implicated in caloric restriction, oxidative stress, aging, and various human diseases. Emerging evidence has found dysregulation of mitochondrial sirtuins in multiple dermatological conditions, including responses to ultraviolet radiation (UVR), suggesting their importance in maintaining skin health. In this review, we discuss the roles and implications of mitochondrial sirtuins in cutaneous cellular processes, and their emerging potential as a target for the management of skin diseases, including skin cancer. Among mitochondrial sirtuins, SIRT3 is the most studied and linked to multiple skin conditions and diseases (keratinocyte differentiation, wound healing, chronological aging, UVR and ozone response, systemic sclerosis, melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC)). SIRT4 has been connected to keratinocyte differentiation, chronological aging, UVR response, alopecia, BCC and SCC. Further, SIRT5 has been associated with keratinocyte differentiation, melanoma, BCC and SCC. Overall, while there is compelling evidence for the involvement of mitochondrial sirtuins in skin, additional detailed studies are needed to understand their exact roles in skin and skin cancers.

Graphical Abstract

Mitochondrial sirtuins (SIRTs −3, −4, and −5) have been implicated in caloric restriction, oxidative stress, aging, and various human diseases. Emerging evidence has found dysregulation of mitochondrial sirtuins in multiple dermatological conditions, including responses to ultraviolet radiation (UVR), suggesting their importance in maintaining skin health. In this review, we discuss the roles and implications of mitochondrial sirtuins in cutaneous cellular processes and their emerging potential as a target for the management of skin diseases. In this graphical abstract, the involvement of SIRTs −3, −4, and −5 are indicated in multiple dermatological conditions including skin cancer.

Keywords

mitochondrial sirtuins; ultraviolet radiation; skin; skin cancers

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CONFLICT OF INTEREST

The authors state no conflict of interest.

INTRODUCTION

The founding member of the nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylase (HDAC) sirtuin family, Sir2, was described initially in *S. cerevisiae* and was associated with stress response and longevity (1). Since then, Sir2 homologs have been identified in numerous species, and mammalian sirtuins have been found to play key roles in cellular processes such as metabolism, cell cycle, transcriptional regulation, and cell division, as well as the pathogenesis of a variety of diseases, including cancer (2-4). There are seven known mammalian sirtuins (SIRTs 1 to 7), and all of them have a conserved Sir2 catalytic core domain, which is key in their NAD^+-dependent deacetylase activity (5). Each sirtuin has been found to have distinct subcellular localizations, as well as discrete protein deacetylation or other catalytic activities (6, 7). Although certain sirtuins may be found throughout the cell, their localization and site of action allows each sirtuin to have distinct functions within cells. SIRT1 and SIRT2 are primarily found in the nucleus and cytoplasm, respectively, although certain cellular conditions may cause their localization to the other cellular compartments (8, 9). SIRT3, SIRT4 and SIRT5, which we will focus on in this review, are referred to as the mitochondrial sirtuins, as they are located primarily in the mitochondria. Their localizations suggest that they are principally involved in metabolism, although they may have other effects within the cell (10). SIRT6 and SIRT7 are found in the nucleus, where they facilitate transcription and epigenetic regulation (11).

While SIRT3, SIRT4 and SIRT5 are predominantly localized in the mitochondria, each has a unique catalytic activity and contributes to mitochondrial homeostasis via distinct mechanisms. SIRT3, the most studied mitochondrial sirtuin, is one of the key mitochondrial deacetylases in regards to regulation of energy production (12). SIRT4, on the other hand, shows weak deacetylation activity (13), and behaves as a deacylase (14), lipoamidase (15) and ADP-ribosyltransferase (16). SIRT5 also has weak deacetylation activity (17), and is active as a lysine demalonylase, desuccinylase (18) and deglutarylase (19). Due to their distinct catalytic activities, mitochondrial sirtuins have been found to be involved in a number of diverse pathways (20), and their dysregulation has been observed in multiple metabolic and aging-related diseases, including skin conditions and skin cancers (21).

ROLE OF MITOCHONDRIAL SIRTUINS IN SKIN AGING AND IN RESPONSE TO UVR AND OZONE EXPOSURE

As the primary barrier between the human body and the environment, the skin is constantly exposed to damages from environmental factors as well as biological mishaps. Mitochondrial sirtuins have been implicated in the skin's response to many of these hazards, including the external factors such as ultraviolet radiation (UVR), as well as internal factors such as aging. Below, we discuss the roles that have been uncovered for mitochondrial sirtuins in the skin aging and in response to UVR and ozone exposure. (Figure 1, Table 1).

Role in chronological skin aging

Skin aging is a complicated process involving both intrinsic and extrinsic factors and is accompanied by a loss of morphologic and physiologic characteristics. There are two main, distinct types of aging scenarios that affect the skin: chronological skin aging and photoaging. Chronological aging is a spontaneous process that proceeds with elapsed time, and throughout the body, mitochondrial sirtuins have been found to play an important role in chronological aging and aging-related diseases (22). For example, in one mouse model, the loss of SIRT3 was found to accelerate the aging process (23). Another study found reduced levels of SIRT3 in various organs and tissues in aged mice, including adipose, kidney, and lung tissues, although no change was seen in the skin (24). Interestingly, an *in vitro* study revealed an upregulation of SIRT4 in human foreskin fibroblasts with increased passage numbers (25), associated with the downregulation of miR-15b, a repressor of SIRT4 mRNA. This study suggested that SIRT4 may be linked to aging in human fibroblasts. Although lack of SIRT5 has been shown to exacerbate aging-related diseases like Parkinson's disease (26), there is so far no data available addressing the role of SIRT5 in skin aging. The scarcity of available research on mitochondrial sirtuins in chronological skin aging makes it difficult to reach a conclusion at this time, though their roles in other aging-related conditions/diseases strongly suggest that SIRT3, SIRT4 and SIRT5 need to be further explored.

Role in ultraviolet radiation (UVR) response and photoaging

Photoaging is premature aging of the skin primarily instigated by frequent UVR exposure (27, 28). Solar UVR that reaches the atmosphere is comprised of 90–99% UVA (320–400 nm) and 1–10% UVB (280–320 nm). Most of the high energy UVR (UVC, 200-290 nm) is absorbed by stratospheric ozone. Both UVA as well as UVB have been implicated in various cutaneous conditions. Indeed, UVR has numerous effects on the skin, both beneficial and harmful. While UVR catalyzes the synthesis of vitamin D in the skin and may be used to treat certain skin disorders like psoriasis, it also is a primary contributor to detrimental processes such as photoaging, DNA damage, and ROS generation (29, 30). A study by Iwahara and colleagues suggested a UVR-responsive role for SIRT3 by showing that in HeLa and U2OS cells, the full-length form of SIRT3 was directly degraded in the nucleus after exposure to UVR (70 J/m^2), which resulted in increased stress-responsive genes (31). Another study found that UV exposure in normal human epidermal keratinocytes (NHEKs) increased mitochondrial reactive oxygen species (mtROS), as well as dysregulated SIRT3 and SIRT4 (32). In this study, NHEKs were exposed to UVB (10 mJ / cm^2) and monitored for up to 10 hours. They observed a sustained reduction of SIRT3 mRNA, although SIRT4 mRNA levels were only transiently reduced at 3 hours and ultimately upregulated by 10 hours (32). Fluctuating SIRT4 levels were reported in another study that employed the broader light spectrum of solar simulated light (SSL, 4.152 J/cm^2 UVA and 193.8 mJ/cm^2 UVB) on NHEKs, where SIRT4 mRNA levels were shown to be increased at 5 hours post-treatment, and maintained it until 8 hours (33). The discrepancy between increased SIRT4 mRNA (by 5 hours) and protein (8 hours and later) is likely due to the time lag between transcription and translation (33). A similar trend was observed in another recent study that found an increase in SIRT4 at 72 hours after UVR (30 mJ/cm^2 of 75% UVB and 25% UVA) (34). Although there is currently no direct evidence linking SIRT5 to photoaging or UVR, it appears that SIRT5 may contribute to the retrieval of cell viability after UVR in

keratinocytes due to its role in glycolysis regulation (35), as the augmentation of glycolysis can recover UV-stressed keratinocytes (60 mJ/cm^2 of 68% UVB and 32% of UVA) (36). Overall, the available data suggest that mitochondrial sirtuins, especially SIRT4 may play a key role in the response of human keratinocytes to UV damage, and may, therefore, be potential targets to combat photoaging. However, more research needs to be done on this subject to fully understand the roles and significance of mitochondrial sirtuins in cutaneous aging, especially in *in vivo* models.

Role in ozone exposure response

Another environmental hazard that the skin is exposed to is ozone. Ozone is a gas that consists of three oxygen atoms (O_3) that naturally occur in the Earth's atmosphere. Interestingly, ozone in the upper atmosphere is beneficial to the skin by blocking harmful UVR from passing through the atmosphere (37). In the last century, depletion of ozone in the atmosphere has increased the amount of UVR that the skin is exposed to and likely has contributed to the heightened incidence of skin cancer (38). Although ozone can be used to treat certain skin diseases (39), atmospheric ozone is categorized as an air pollutant (40). In terms of its interactions with the skin, ozone reacts with lipids on the surface of the skin, generating several inflammable products such as 4-OPA and 6-MHO (41). Together with ozone, these products are able to penetrate skin barrier (42, 41), which has been found to induce inflammation, reduction of antioxidants, and affect mitochondrial ROS in a mouse model (43). Evidence for the mitochondrial sirtuin-related response to ozone was found in a study where ozone (0.8 ppm) exposure to NHEKs was shown to cause a 48.2% reduction in SIRT3 levels (44). This study also found increased H_2O_2 levels, decreased ATP levels, increased DNA damage, and an increased inflammatory response as measured by IL-1α ELISA, suggesting an association between SIRT3 and cellular ozone damage response.

Although no direct study has been done to determine the role of SIRT4 in the skin's response to ozone exposure, it appears that SIRT4 possesses tissue-specific effects on ROS perturbation. For example, SIRT4 induces ROS to accelerate cardiac hypertrophy by inhibiting the activity of MnSOD (45), but suppresses ROS and podocyte apoptosis to protect against diabetic nephropathy (46). A similar lack of studies exploring links between ozone and SIRT5 exists, although this protein may still serve as a guardian of the skin by eliminating ROS. Since it has been reported that SIRT5 was able to desuccinylate SOD1 to eliminate ROS (47), SIRT5 may play a similar role to SIRT3 in ROS scavenging in response to ozone exposure.

ROLE OF MITOCHONDRIAL SIRTUINS IN SKIN AND SKIN DISEASES

Mitochondrial sirtuins are integral to key protective processes employed by the skin against insults generated from environmental factors as well as biological mishaps. Keratinocyte differentiation is one such process. Below, we discuss the roles that have been discovered for mitochondrial sirtuins in keratinocyte differentiation, wound healing as well as in response to autoimmune diseases (Figure 1, Table 1).

Role in keratinocyte differentiation

Keratinocytes make up the largest portion of the epidermal biomass, and are involved in many cutaneous activities, such as skin inflammation (48), protection against UV damage (49), and wound healing (50). Keratinocyte proliferation and differentiation are essential in maintaining a functional and intact epidermis, and successful differentiation requires the involvement of specific molecules and proteins, including mtROS and SIRT3 protein. Increased mtROS has been shown to be involved in the activation of differentiation promoting proteins, including Notch and β-catenin (51). As they differentiate, keratinocytes detach from the basal layer of the epidermis and express early differentiation markers Keratins-1 and −10 (52). Bause *et al.* demonstrated that SIRT3 expression was decreased during keratinocyte differentiation, and the knockdown of SIRT3 in keratinocytes leads to elevated mtROS as well as increased differentiation markers Keratins −1 and −10 (53). Accordingly, overexpression of SIRT3 reversed the process, resulting in decreased mtROS and differentiation markers including loricrin and filaggrin (53). This suggests that SIRT3 is an important regulator of keratinocyte differentiation.

The involvement of mitochondrial sirtuins in keratinocyte differentiation is expected, as keratinocyte metabolism is continuously adjusted during this process. Although there are limited studies regarding the roles of SIRT4 and SIRT5 in keratinocyte differentiation, their roles in energy metabolism suggest they may also have roles in this important process. In one study, SIRT4 was found to be present in NHEK, and its expression was shown to be in opposition to SIRT3, likely due to their opposite roles in metabolism, especially in that SIRT3 activates glutamate dehydrogenase (GDH) while SIRT4 does the opposite (32, 54). However, the role of SIRT4 in differentiation has not been explored. In a different *in vitro* study, Benavente et al. simulated the differentiation process by growing undifferentiated keratinocytes with a media-air interface (33). They observed a transient increase of SIRT4 and SIRT5 expression, with their levels returned to the normal range upon terminal differentiation, suggesting that a transient increase in SIRT4 and/or SIRT5 may be involved in the differentiation process. Interestingly, although no concrete work has been done in keratinocytes, SIRT4 and SIRT5 have been found to regulate the differentiation of adipocytes. In one study, SIRT4 was shown to be upregulated in subcutaneous bovine adipocyte differentiation (55); while another group found that SIRT5 was necessary in the browning of subcutaneous white adipose tissue (56). These findings suggest that mitochondrial sirtuins, especially SIRT3, may be key modulators in the harmony and regulation of cellular differentiation.

Role in wound healing

Cutaneous wound healing is a complex but integrated process involving four distinct phases: homeostasis, inflammation, proliferation, and remodeling (57). A successful wound closure requires a subtle collaboration between the skin cells and non-skin cells, such as blood cells, immune cells, and stem cells. A recent mouse study found that SIRT3 plays an important role in wound repair, especially in wound macrophages (58). This study demonstrated significantly increased SIRT3 in wound macrophages during the transition from an inflammatory to a reparative stage. It was further demonstrated that FAB4, a fatty acid-binding protein, was inversely correlated with SIRT3 in wound macrophages (58). Further,

the SIRT3 deficient mice displayed impaired wound repair. In addition, the wound macrophages isolated from SIRT3-deficient mice showed an increase in pro-inflammatory factors IL1β, Tnfα, and Nos2, which were reversed by the adoptive transfer of macrophages from SIRT3-competent mice, resulting in improved healing (58). In addition, this study also found that under pre-diabetic conditions, SIRT3 was decreased in wound macrophages, likely due to the upregulation of FAB4, which resulted in sustained secretion of pro-inflammatory factors (58). Another group found that the administration of MC2562, a SIRT3 activator, accelerated the process of wound healing in mice (59). However, this acceleration may not primarily result from the activation of SIRT3, as MC2562 also activates SIRT1 and SIRT2, albeit at higher concentrations (6). There has been no work done on wound healing in the other mitochondrial sirtuins, although their roles in cellular metabolism suggest that they may be involved and should be explored further.

Role in fibrotic and scarring diseases

Systemic sclerosis (SS), also known as scleroderma, is a rare autoimmune disease characterized by vasculopathy and fibrosis of the skin and internal organs, with a 74.9% five-year survival rate from diagnosis (60). SS is marked by the replacement of normal skin tissues with extracellular matrix and collagen, as well as decreased expression of collagenase in skin fibroblasts (61). Although the exact etiology of SS is unknown, abnormalities in several cell signaling events have been implicated in the fibroblasts of SS patients, including cytokines and growth factors (62), as well as SIRT3 signaling (63). In a mouse study, SIRT3 knockout was found to promote tissue fibrosis in multiple organs through induction of fibroblastic TGF-β (64), a critical signaling molecule in SS and other fibrotic diseases involved in the production of the extracellular matrix (65). In a study by Akamata et al., SIRT3 was found to be reduced in SS skin biopsies and was associated with increased ROS and TGF-β-induced fibrotic gene expression (66). Further, it was also found that induction of SIRT3 by a novel fluorinated synthetic honokiol analogue hexafluoro or genetic overexpression attenuated mtROS and TGF-β expression, while overexpression of TGF-β in normal fibroblasts lead to reduced SIRT3 and increased ROS (66). Therefore, SIRT3 appears to have potential anti-fibrotic roles in SS fibroblasts, and the activation of SIRT3 may be a therapeutic strategy in the treatment of SS through inhibition of the TGF-β pathway. This appears to be a different regulatory mechanism from the macrophage-based SIRT3 modulation that occurs during wound healing, suggesting that SIRT3 is linked to multiple skin healing pathways.

Although there have been no reports of SIRT4 in SS, this sirtuin has been suggested to play a role in other fibrosis-involved diseases, such as central centrifugal cicatricial alopecia (CCCA). CCCA is common in African American females and is marked by hair loss (primarily in the central part of the scalp) and scarring alopecia marked by activation of fibroblast (66). In a transcriptome analysis of scalps from five CCCA patients, SIRT4 was found to be downregulated, indicating a potentially protective role of SIRT4 in CCCA (67). However, this data is far from conclusive, and further research is needed to investigate the roles of SIRT4 and the rest sirtuins in CCCA and other fibrosis-related diseases that can affect the skin.

ROLE OF MITOCHONDRIAL SIRTUINS IN SKIN CANCERS

The known functions of mitochondrial sirtuins in metabolism and energy production point towards their possible roles in cancer progression. However, the role of mitochondrial sirtuins in cancer appears to be complex, with evidence suggesting both tumor promoter and suppressor functions. The conflicting evidence based on a number of studies suggests that all three mitochondrial sirtuins can act either as a tumor suppressor or as a tumor promoter, likely depending on the cellular and/or tissue context. This has been discussed further in several recent reviews (68-70), and persists in the context of skin cancer as well.

Skin cancers are the most common human cancer, and its main types are divided into melanoma and non-melanoma skin cancer (NMSC), which includes basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC). UV exposure has been identified as one of the major epidemiologic risk factors of all three types of skin cancer (29), as UV-induced DNA photoproducts can be highly mutagenetic (71). In addition to DNA mutations, epigenetic abnormities and altered cellular metabolism exist widely in skin cancer, providing a rationale for the role of the mitochondrial sirtuins in cutaneous neoplasms. Below, we discuss the roles for mitochondrial sirtuins that have been observed in the three main types of skin cancers (Figure 1, Table 1).

Role in melanoma

Arising from the melanocytes in the epidermis, melanoma is one of the deadliest types of skin cancer, and its incidence has been increasing over the past 30 years (72). Environmental and behavioral changes are likely responsible for this, with increased UVR exposure leading signature UV-mediated C→T base pair conversions. As the most frequently mutated gene in melanoma, BRAF mutations exist in over 50% of melanoma patients (73, 74). The BRAF mutation has two major roles in the progression from normal skin to melanoma: 1) it initiates the genesis of nevi from melanocytes (75) and 2) it then cooperates with subsequent driver mutations, such as TERT (76) and/or p53 (77), to promote the transition from nevi to melanoma.

The involvement of mitochondrial sirtuins in melanoma development and progression is not very well understood. Recently, we have demonstrated that SIRT3 may act as a tumor promoter in melanoma (78). In our study, we found that SIRT3 is significantly overexpressed in human melanoma cell lines as well as clinical melanoma tissue samples. Additionally, knockdown of SIRT3 by small hairpin RNA resulted in decreased cell growth, G1-phase cell cycle arrest and senescence induction, as evidenced by increased senescence-associated beta-galactosidase activity and p16 and p21 protein expression in melanoma cell lines. Moreover, forced overexpression of SIRT3 promoted the proliferation of melanoma cells as well as normal immortalized Mel-ST melanocytes. In a xenograft mouse model, knockdown of SIRT3 inhibited tumor growth and improved overall survival rate, emphasizing the potential tumor promotor role of SIRT3 in melanoma (78). The tumor promotor role of SIRT3 is also supported by a very recent study by Torrens-Mas et al., where the authors found that mutant p53 induces SIRT3/MnSOD axis to moderate ROS production in melanoma (79). In this study, the mutant p53 in MeWo melanoma cells was shown to promote SIRT3, which enhanced the activity of manganese superoxide dismutase

(MnSOD), leading to a tempered ROS level that helps the melanoma cells survive the cytotoxic ROS environment. In a separate study from our laboratory, we demonstrated the effect of 4'-bromo-resveratrol, a dual SIRT1 and 3 inhibitor (80), against human melanoma cells (81). In this study, we found that 4'-bromo-resveratrol treatment imparted antiproliferative effects against human melanoma cells through metabolic reprogramming and effects on the cell cycle and apoptosis signaling. This further confirms the tumor promoter role of SIRT3 in melanoma (81).

The role of SIRT4 in melanoma, on the other hand, has not been explored other than a study that found an upregulation of SIRT4 in melanoma after administration of melphalan, a chemotherapy drug (82). Consistent with the tumor suppressor vs. promoter debate in other cancers, there are differing studies regarding the role of SIRT5 in melanoma. In one study, knockdown of SIRT5 decreased the proliferation of melanoma cells both *in vivo* and *in vitro* (83). However, another study using a $BRAF^{V600E}$ mouse model showed that SIRT5 knockout did not affect melanoma development or progression (84). Therefore, additional research is needed to understand the exact roles of SIRT4 and SIRT5 in melanoma.

Role in basal cell carcinoma (BCC)

BCC of the skin is derived from keratinocytes located in the basal layer of the epidermis, and is the most common human cancer, with millions of people affected by this neoplasm every year in the United States (85). Although low in metastatic and mortality rates, BCC can be associated with significant morbidity, and patients diagnosed with this neoplasm are at a greater risk for developing melanoma (86). Similar to melanoma, UV is a major environmental carcinogen of BCC. UV-mediated C→T conversions are observed in several tumor suppressor genes in BCC patients, including patched 1 (PTCH1) and p53 (88). Although direct research on mitochondrial sirtuins and their response to UV in this neoplasm are severely lacking, the links between SIRT3 and p53, especially those discussed above in the melanoma section, suggest that further research will uncover a clear relationship in BCC. In a recent epidemiology study, it was found that people receiving a high level of occupational UV exposure were associated with an increased risk of BCC (87). In this paper, Temel et al. sampled both BCC and normal skin biopsies from patients, and analyzed the mRNA expressions of all the sirtuins (89). For the mitochondrial sirtuins, they found that SIRT3 mRNA was decreased in BCC samples as compared to normal tissues, suggesting a tumor-suppressive role for SIRT3 in BCC. SIRT4 and SIRT5 were found to have no change between normal and BCC tissues, which suggests they may not be involved in BCC progression, although significantly more research needs to be done on all three mitochondrial sirtuins to better elucidate their mechanisms in BCC.

Role in squamous cell carcinoma (SCC)

Depending on its anatomic site, SCC can be separated into four sub-types: cutaneous SCC (cSCC), head and neck SCC (HNSCC), esophageal SCC (ESCC), and lung SCC (LUSC) (90). Although they can all be classified as SCC, the only cSCC is classified as skin cancer and will be discussed here. cSCC is a neoplasm of keratinocytes arising from the squamous layer of the epidermis and is the second most common skin cancer in the United States with a trend of increasing incidence (91, 85). Similar to BCC, UV exposure is the major cause of

cSCC (92). A UV signature characterized by C→T conversions exists in most cSCC patients (93), but whether this is related to mitochondrial sirtuins are unknown. Interestingly, to date, the only evidence that exists for all three mitochondrial sirtuins suggests that they play a tumor promotor role in cSCC (33). The research compared sirtuin expression of actinic keratosis, a pre-cSCC lesion, and cSCC biopsies to their normal adjacent skin, and found that SIRT3, SIRT4 and SIRT5 were upregulated in both actinic keratosis and cSCC. Although the evidence points towards a potential tumor promotor role for the mitochondrial sirtuins in cSCC, more extensive *in vitro* and *in vivo* research is needed to draw any definitive conclusions.

CONCLUSIONS

Mitochondrial sirtuins have been found to play important roles in maintaining skin homeostasis against environmental stress, and the alteration of mitochondrial sirtuins is closely related to skin dysfunctions and cancers. The finding that SIRT3, SIRT4 and SIRT5 are dysregulated in several dermatological conditions may provide us avenues to maintaining skin health. Additionally, the dysregulation of these sirtuins in skin diseases and cancers may provide an opening to develop new therapeutic strategies. However, the mechanism of mitochondrial sirtuins in dermatological conditions has not been fully discovered, especially that of SIRT4 and SIRT5. Therefore, future research is needed to uncover the functional relevance of mitochondrial sirtuins in skin diseases, including skin cancer.

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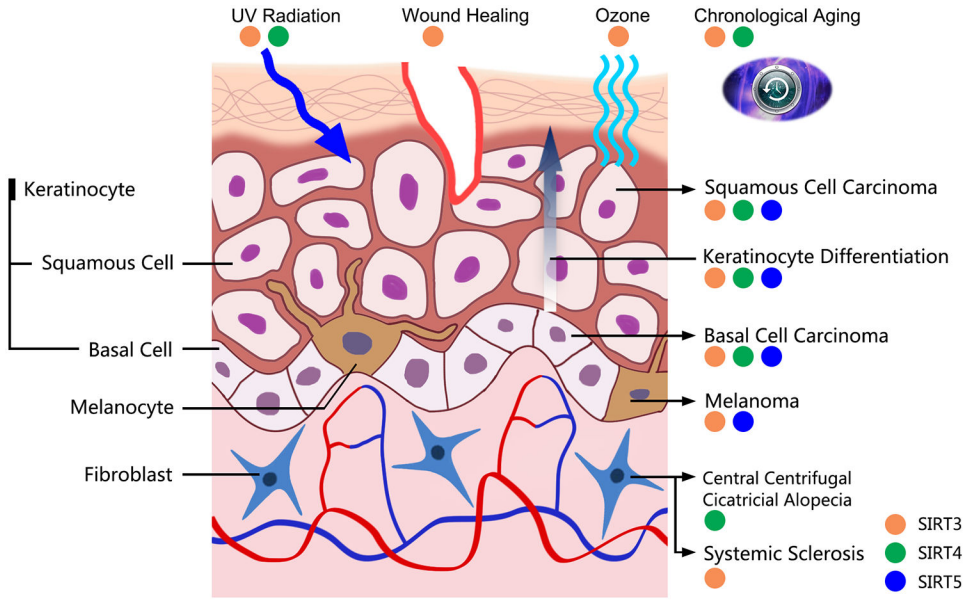

Figure 1. The involvement of mitochondrial sirtuins in skin and skin cancers.

Mitochondrial sirtuins have been studied in several skin conditions and diseases. SIRT3 is involved in keratinocyte differentiation, wound healing, chronological aging, UV radiation/ozone response, Systemic Sclerosis, melanoma, basal cell carcinoma, and squamous cell carcinoma. SIRT4 has been associated with keratinocyte differentiation, chronological aging, UVR response, central centrifugal cicatricial alopecia, basal cell carcinoma, and squamous cell carcinoma. SIRT5 has been implicated in keratinocyte differentiation, melanoma, basal cell carcinoma, and squamous cell carcinoma.

Table 1.

The expression level and molecular associations of mitochondrial sirtuins in skin and skin cancers.

Condition/Disease	SIRT3	SIRT4	SIRT5	Molecular Association
Keratinocyte Differentiation	↓	↑	↑	Keratin-1 and −10, loricrin, filaggrin, mtROS
Wound Healing	↓	Unk	Unk	IL1β, FAB4
Chronological Aging	↓	↑	Unk	miR-15b
UV Radiation	↓	↑	Unk	mtROS
Ozone	↓	Unk	Unk	IL-1α, mtROS
Systemic Sclerosis	↓	Unk	Unk	TGF-ß, mtROS
Central Centrifugal Cicatricial Alopecia	Unk	↓	Unk	Unk
Melanoma	↑	Unk	↑↓	P16, P21, MnSOD, mtROS
Basal Cell Carcinoma	↓	-	-	Unk
Squamous Cell Carcinoma	↑	↑	↑	Unk

Unk, Unknown; -, No change; ↑, Upregulated; ↓, Downregulated