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REVIEW ARTICLE

UVB Induced Skin Cancer Development in Experimental Mouse Model: A Review

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Abstract Skin cancer is a widespread global issue, with ultraviolet (UV) radiation being a significant risk factor. Researchers often use the mouse skin cancer model to develop novel therapeutic chemoprevention strategies. This model involves exposing mice to UVB radiation to induce skin cancer. In most studies, hairless mice were often used for their resemblance to human skin. However, using hairless mice is costly. Therefore, as researchers look into a more cost-effective model as an alternative to be adapted for skin carcinogenesis studies, in this review, we summarised that 69.57% of studies used female SKH-1 hairless mice, 17.39% used BALB/c mice, 8.69% used Swiss albino mice, and 4.35% used HRS/J hairless mice. All studies used mice aged 5-8 weeks. Different models of mice were irradiated with various doses of UVB. SKH-1 hairless mice received UVB radiation twice a week for 10-18 weeks, while Swiss albino mice were exposed to UVB radiation three times a week for 30 weeks. HRS/J hairless mice received UVB radiation five times a week for 15 weeks. BALB/c mice were treated with DMBA and exposed to UVB radiation for 10-16 weeks to induce skin tumors. In conclusion, we can suggest adapting female BALB/c mice, aged 6-8 weeks, treated with DMBA and exposed to 180 mJ/cm^2 UVB radiation three times a week for 16 weeks for the UVB-induced skin cancer model, as it is more cost-effective than other hairless mouse models.

Keywords: Mice model, carcinogenesis, chemoprevention, skin cancer, UVB.

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Introduction

Skin cancer is a serious health concern that is increasing globally [1]. A multi-step process that ends in the development of malignant skin tumors by a series of distinct phases is shown in Figure 1. Skin cancer begins with initiation, a reversible mechanism brought on by genetic alterations, gene activation, or gene inactivation. Tumor promotion is the next step of carcinogenesis, and it contributes to the growth of benign skin lesions called pre-neoplastic papilloma. Vascular permeability, the initial stage of angiogenesis in skin tumors, occurs concurrently with tumor promotion. Pre-neoplastic lesions grow blood vessels to provide oxygen and other nutrients in a multi-step process. According to Robertson [2] tumor progression is the next stage of carcinogenesis, which occurs when genetic mutations accumulate, resulting in the transformation of pre-malignant skin lesions into cancer, that is most commonly squamous cell carcinomas. Additionally, changes in the expression profiles of particular proteins have been linked to skin cancer [3, 4].

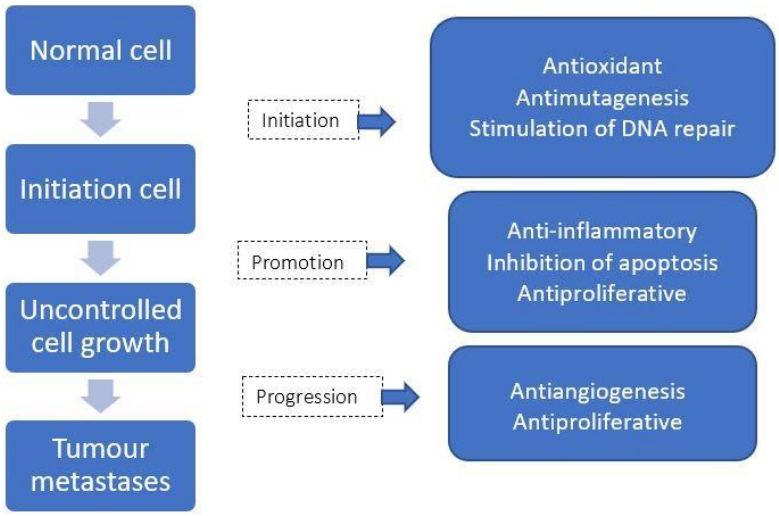

Figure 1. The mechanisms of potential chemoprevention during the development of cancer

UV radiation is a critical cancer-causing substance and the leading initiator of skin cancer [5]. UVA and UVB from the sun, at wavelength 320–400 nm and 280–320 nm, respectively, penetrate the atmosphere and reach the earth's surface. UV radiation from the sun causes cutaneous DNA damage, and initiates skin cancer [6]. UV energy can be classified into three components based on their electrophysical properties: UVA, UVB, and UVC. UVC photons have the highest energy and shortest wavelengths (100-280 nm), while UVA photons have the least energy and longest wavelengths (315-400 nm). UVB photons have wavelengths that fall in between those of UVC and UVA (280-315 nm). However, these UV components can damage cells, tissues, and molecules by causing oxidative damage, base modifications, and mutations. In exposed mouse skin, UVB irradiation causes epidermal hyperplasia, which precedes toward benign papilloma, and then evolves into squamous cell carcinoma. UV has a variety of effects on skin physiology, some of which are immediate and others which are delayed. Inflammation is one of the most distinct acute effects of UV exposure on the skin. UVB triggers inflammation and "sunburn" by activating a cascade of vasoactive, cytokines, and neuroactive skin intermediaries [7]. If the UV dose surpasses the damage response threshold, keratinocytes will set off apoptotic pathways, resulting in cell death. Apoptotic keratinocytes, known as “sunburn cells” can be distinguished by their pycnotic nuclei [8]. UV exposure also leads to an epidermal thickness increase called hyperkeratosis. UV causes harmful reaction pathways in keratinocytes by causing cell injury. Epidermal keratinocytes proliferate vigorously, mediated by different epidermal growth factors, several hours after UV penetration and injury response signals have faded [9]. After UV exposure, increased keratinocyte cell division causes an accumulation of epidermal keratinocytes, which thickens the epidermis. When epidermal hyperplasia is present, the skin is well covered against UV penetration [10]. Adaptive melanisation of the skin, seen as tanning, occurs in conjunction with epidermal hyperkeratosis. According to Mitra and Fisher [11] UV exposure increases melanin pigment synthesis and epidermal accumulation in the skin. Defects in this essential physiologic response, shielding the skin from UV injury, can cause a higher risk of skin cancer. While ambient sunlight is primarily a combination of both UVA/UVB, they may have distinct impacts to the skin. For instance, UVB act as powerful initiator do induce inflammation and production of DNA photolesions [12], while UVA is a compelling source of free radical that causes oxidative damage to DNA and other macromolecules [13]. As a result, each can lead to carcinogenesis in different ways [14].

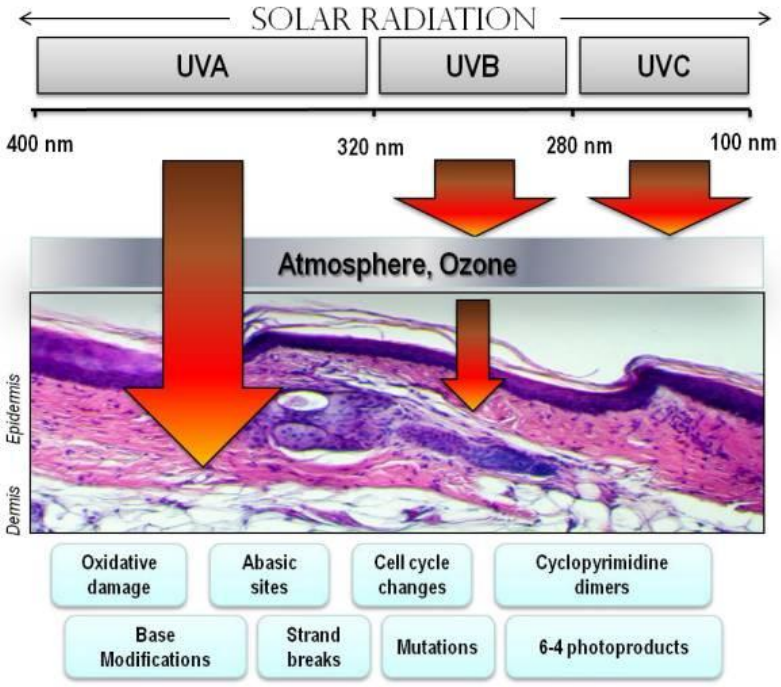

Figure 2. Solar radiation's biological impact on the skin [5]

In order to prevent or lower the risk of UVB-induced skin cancer, many researchers have researched the chemoprevention effects of natural and synthetic chemicals over the years. Chemoprevention may involve the use of drugs, vitamins, minerals, or other agents that can interfere with the development or progression of cancer cells [15]. The most common UVB skin carcinogenesis model used was using female hairless mice. Due to their appropriateness as animal model that closely reflects human skin responses to acute UV exposure, hairless mice are frequently used in UVB skin investigations [16]. Key anatomical and cellular responses seen in human skin after UV exposure have been documented in the hairless SKH-1 mice employed in these investigations [16]. Due to their commonality, UVB radiation's effects on the skin may be studied, and prospective interventions or therapies can be evaluated.

However, UVB-induced skin cancer studies using hairless mice can be costly for genetically modified mice more susceptible to developing skin cancer, such as the hairless SKH-1 mice. Comparatively speaking, albino mice are easier to find and more cost-effective than hairless mice. This is because hairless mice are a particular genetic strain with no hair because of a defect in the route where hair follicles grow. These mice are frequently used in scientific investigations, including wound healing, skin disorders, and hair follicle biology [17]. However, despite the costs and availability, studying UVB-induced skin cancer in mice remains an imperative research tool for understanding the mechanisms of skin cancer development and testing potential chemopreventive agents or therapies. Therefore, in this review, we review past articles on chemoprevention in UVB-induced skin cancer studies to find a more cost-effective model to adapt for future studies, which include mouse type, gender & UVB dose for inducing skin carcinogenesis.

Methodology

Recent articles were collected and consulted to conduct this research on the prevention of UVB-induced skin cancer/carcinogenesis. Various journals and electronic databases, including PubMed, Elsevier, Google Web, Google Scholar, Web of Science, and Springer, were utilised to gather information related to this plant. The study focused only on texts written between January 2013 and February 2023. The search was conducted using keywords such as 'chemoprevention', 'UVB', 'UVB-induced', 'skin cancer', 'skin carcinogenesis', and 'mouse model'.

Results and Discussion

Gender of Mouse

According to Table 1, there are similarities in the mouse type used. About 73.91% of the studies used SKH-1 hairless mice (female) aged 5 to 8 weeks for experimental carcinogenesis studies. If an experiment requires a long exposure duration, it is recommended to use female mice instead of male mice. This is because male mice tend to gnaw on tumor sites, which can increase inflammation and affect the accuracy of the results. Additionally, tumor-bearing female mice can be housed together in a cage (assuming it is large enough). In contrast, male mice are more aggressive and are at higher risk of injuring each other. Many studies generally prefer females because they are much less likely to fight, so there are less wounding and scarring that can complicate observations.

Table 1. Summation of UVB-induced skin carcinogenesis animal model

Animal			UVB-induced skin carcinogenesis model		References
	Gender (M/F)	Age (weeks)	Dose	Exposure	
SKH-1 Hairless Mice	F	5	180 mJ/cm^2 UVB	Twice weekly for 28 weeks.	[18] Singh *et al*., 2018
TSP1-Null Mice SKH-1	Not mentioned	6-8	224 mJ/cm^2 UVB	Thrice weekly for 22 weeks.	[19] Mirzoeva *et al*., 2018
SKH-1 hairless mice	F	5-8	15.4 kJ/m^2 UVA with 1.2 kJ/m^2 UVB (increasing 10% weekly until dose of 38.5 kJ/m^2 UVA and 2.8 kJ/m^2 UVB reached at week 10, cumulative dose of 427 kJ/m^2 UVA and 33 kJ/m^2 UVB (week 15)	Thrice weekly.	[20] Dickinson *et al*., 2016
SKH-1 hairless mice	F	6-8	15.4 kJ/m^2 UVA with 1.2 kJ/m^2 UVB (increasing 10% weekly until dose of 38.5 kJ/m^2 UVA and 2.8 kJ/m^2 UVB reached at week 10, cumulative dose of 427 kJ/m^2 UVA and 33 kJ/m^2 UVB (week 15),	Thrice weekly.	[21] Blohm-Mangone *et al*., 2018
SKH-1 hairless mice	F	6	Initial dose of 50 mJ/cm^2, increase 25 mJ/cm^2 weekly to 150 mJ/cm^2,	Thrice weekly for 25 weeks.	[22] Huang *et al*., 2017
SKH-1 hairless mice	F	6-8	Initial dose of 36 kJ/m^2 UVA and 1.8 kJ/m^2 UVB, increasing 10% weekly. At week 6, the dose reached 60 kJ/m^2 UVA and 2.9 kJ/m^2 UVB (maintained from week 6 until week 15)	15 weeks.	[23] Gao *et al*., 2017
SKH-1 hairless mice	F	5	2.4 x 10^{-4} W/cm^2 UVA and 1.8 x 10^{-3} W/cm^2 UVB,	5 days per week for 10 weeks.	[24] Ngo, 2018
SKH-1 hairless mice	Not mentioned	Not mentioned	Primary dose of 80 mJ/cm^2 UVB (week 1), followed by a weekly 10% increase until amount of 100 mJ/cm^2	Thrice weekly for 27 weeks.	[25] Qiang *et al*., 2017
SKH-1 hairless mice	Not mentioned	5	90 mJ/cm^2 UVB	5 times/week for 25 weeks (SKH-1, p53$^{+/+}$, p53$^{+/-}$). thrice weekly for 25 weeks (p53$^{-/-}$).	[26] Rigby *et al*., 2017
HRS/J hairless mice	F	20	230 mJ/cm^2 UVB	16 min, 5 times/week, for 15 weeks.	[27] Carrara *et al*., 2019

Animal			UVB-induced skin carcinogenesis model		References
SKH-1 hairless mice	Not mentioned	5-6	600 mJ/cm^2 UVB	Twice weekly for 10 weeks.	[28] Hou *et al*., 2018
Swiss albino mice	M	Not mentioned	180 mJ/cm^2 UVB	Thrice weekly for 30 weeks.	[29] Chandrakesan *et al*., 2018
SKH-1 hairless mice	F	6	180 mJ/cm^2 UVB	Thrice weekly for 24 weeks.	[30] Boakye *et al*., 2016
SKH-1 hairless mice	F	6-8	180 mJ/cm^2 UVB	Twice weekly for 30 weeks.	[31] Chaudhary *et al*., 2017
SKH-1 hairless mice	F	6	180 mJ/cm^2 UVB	Thrice weekly for 22 weeks.	[32] Lee *et al*., 2017
SKH-1 hairless mice	F	8	30 mJ/cm^2 UVB	Twice weekly for 18 weeks.	[33] Kalin *et al*., 2019
SKH-1 hairless mice	F	4-6	150 mJ/cm^2 UVB	Thrice weekly for 28 weeks.	[34] Hoesseini *et al*., 2019
Fat-1 +/− SKH-1 hairless mice	F	Not mentioned	180 mJ/cm^2 UVB	Thrice weekly for 23 weeks.	[35] Yum *et al*., 2017
Swiss albino mice	Not mentioned	6	180 mJ/cm^2 UVB	Thrice weekly for 30 weeks.	[36] Gunaseelan *et al*., 2019
BALB/c mice	M	6	180 mJ/cm^2 UVB	200 nmol L^{-1} DMBA, thrice weekly for 16 weeks.	[37] Zhao and Zhang, 2015
BALB/c mice	F	6	180 mJ/cm^2 UVB	Twice weekly for 16 weeks.	[38] Tanveer *et al*., 2023
BALB/c mice	F	6	360 mJ/cm^2 UVB	DMBA for 65 times.	[39] Hussaana, 2013
BALB/c mice	F	4	UVB exposure (465 mJ/m^2/day)	5 times per week for 12 weeks.	[40] Listyawati, 2015

Mouse Types

Findings showed SKH-1 hairless mouse is the most commonly used animal model for researching skin cancer caused by UVB radiation, as its pathological and histological characteristics are comparable to those found in non-melanoma skin cancers in humans [41]. This mouse model's development of non-melanoma skin cancer has been found to closely resemble human development, making it a valuable tool for investigating the prevention of photocarcinogenesis [42]. Because of SKH-1 hairless skin, carcinogens, chemopreventive agents, and chemotherapeutical compounds can effortlessly be applied. These mice are immunocompetent and unpigmented, allowing for easy skin stimulation, administration of topical compounds, irradiation to UVB, and visualisations [43]. As a result, the skin cancer development in SKH-1 mice has been extensively investigated and is generally understood [44]. Furthermore, the tumors induced in these mice are morphologically and molecularly similar to UVB-induced skin cancers in men. Apart from the SKH-1 mice, 17.39% used BALB/c mice and 8.69% used Swiss albino mice to establish a skin carcinogenesis model. Removal of the mice's dorsal hair in this

model is crucial, and in the remaining HRS/J mouse model, they are only suitable for skin chemoprevention study during the 3rd week of life; when shading occurs, the mice began to become naked. However, the cost of SKH-1 mice is prohibitively high, and lesser availability compared to albino mice, necessitates an alternative approach to continue studying UVB-induced skin cancer on a more cost-effective research budget. Based on our summary, a cheaper alternative is we can suggest the second most used mouse type, which is BALB/c mice for UVB-induced skin cancer studies.

UVB Radiation Doses

In terms of UVB-induced skin carcinogenesis, UVB exposure ranging from 30 mJ/cm^2 (18 weeks) to 600 mJ/cm2 (10 weeks) twice weekly in SKH-1 hairless mice models causes skin tumors. According to our understanding is that the solar-simulated UV contains 30 mJ/cm^2 UVB. The Swiss albino mice model, on the other hand, was irradiated with 180 mJ/cm^2 UVB thrice weekly for 30 weeks, while HRS/J hairless mice were exposed with 230 mJ/cm^2 UVB for 16 minutes, five times/week, for 15 weeks. Interestingly, the BALB/c mice model was used with or without DMBA as an initiator on top of UVB irradiation ranging from 180-360 mJ/cm^2 for 10-16 weeks. Due to their lower susceptibility to forming skin tumors than SKH-1 hairless mice, these strains were given higher doses and exposed for extended periods. Based on Table 1 summary, a UVB dose of 180 mJ/cm^2 thrice weekly for 16 weeks is most likely suitable for adaptation in future studies.

Conclusions

To summarise the findings of our review on UVB-induced skin cancer models, we have identified that using female BALB/c mice aged 6-8 weeks treated with 200 nmol L^{-1} DMBA as initiator and exposed to 180 mJ/cm^2 UVB radiation 3 times a week for 16 weeks is the most likely cost-effective model approach. This model effectively induces skin cancer and is more cost-effective and easier to find than the hairless mouse models. Our review suggests that researchers consider using this model for their studies on UVB-induced skin cancer. Furthermore, using female BALB/c mice in this model has several advantages, including ease of handling (female vs male) and wider availability than hairless mice. Additionally, this model has been used in several previous studies, allowing for more significant results comparability between different research groups. It is also crucial to remember that the model's parameters could need to be altered based on the research problem being addressed. Nonetheless, we believe that the BALB/c mouse model with the recommended parameters is a viable option for researchers seeking to investigate the mechanisms of UVB-induced skin cancer.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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The conceptualisation and data analysis for the study were conducted jointly by Muhammad Wahizul Haswan Abdul Aziz and Ahmad Rohi Ghazali. Dayang Fredalina Basri contributed important insights to the discussion. The manuscript was written and revised by Muhammad Wahizul Haswan Abdul Aziz, Siti Fathiah Masre, and Ahmad Rohi Ghazali. All authors carefully reviewed and made significant revisions to the manuscript, and approval for the final version.

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