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Ultraviolet A Irradiation on the Eye Induces Non-Melanoma Skin Cancer

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Abstract

Ultraviolet (UV) A irradiation induces skin cancer. This study aimed to investigate the effect of UVA irradiation on the eyes, using a mouse model of non-melanoma skin cancer induction. We administered UVA irradiation in the eyes of mice for thrice per week for 15 weeks after application of 7,12-dimethylbenz[a]anthracene (DMBA). Mice receiving UVA irradiation in the eyes developed skin cancer and their plasma levels of reactive oxygen species (ROS) and corticosterone increased. Furthermore, increased UVA-induced ROS induced the effects of DMBA in a chronic manner; moreover, immunosuppression by corticesterone and Langerhans cells were considered to have induced skin cancer. Immunosuppression may have an important role in the genesis of skin cancer upon UVA/eye-irradiation and DMBA application.

Keywords: Ultraviolet A; 7,12-dimethylbenz[a]anthracene; Reactive oxygen species; Corticesterone; Skin cancer

Introduction

Skin cancers are of various types. Cancers occurring at the sites chronically exposed to sunlight include actinic keratosis, squamous cell cancers, basal cell carcinoma, and melanoma. Ninety percent of skin cancers, except for melanoma, are associated with exposure to ultraviolet (UV) radiation, which causes direct or indirect DNA damage. Usually, damaged DNA is repaired; however, continuous DNA damage results in mutagenesis, thereby resulting in tumorigenesis [1].

We previously investigated the effect of UV irradiation in the eyes on the whole body. However, the effects of UV irradiation in the eyes on the genesis of non-melanoma skin cancer are unclear. This study aimed to investigate the effect of UVA irradiation in the eyes, using a mouse model of non-melanoma skin cancer induction, *via* continuous UVA irradiation following the application of 7,12-dimethylbenz[a]anthracene (DMBA).

Materials and Methods

All animals were treated in accordance with the guide for the care and use of laboratory animals of Suzuka university of Medical Science (approval number: 34). All surgeries were performed under pentobarbital anesthesia, and efforts were made to minimize animal suffering.

Specific-pathogen-free, 6-weeks-old male hairless mice (SLC, Hamamatsu, Shizuoka, Japan) were used. Immunosuppression was initiated in mice *via* topical application of 100 mg of DMBA on the dorsal skin. While DMBA is not directly associated with any cancers, its strong tumorigenic potential has been confirmed [2]. Two weeks after initiation, the mice were placed under light nembutal anesthesia (Dainippon Sumitomo Pharma., Osaka, Japan), and the eye or dorsal skin was locally exposed to UVA (320-400 nm) using a UV lamp (FL20SBLB-A, Toshiba Co., Tokyo, Japan) for 90 ml/cm^2 at one side thrice a week for 15 weeks [3]. After collecting data on tumors (mean number of tumors per mouse) on the final day of examination, we extracted blood and skin samples under anesthesia.

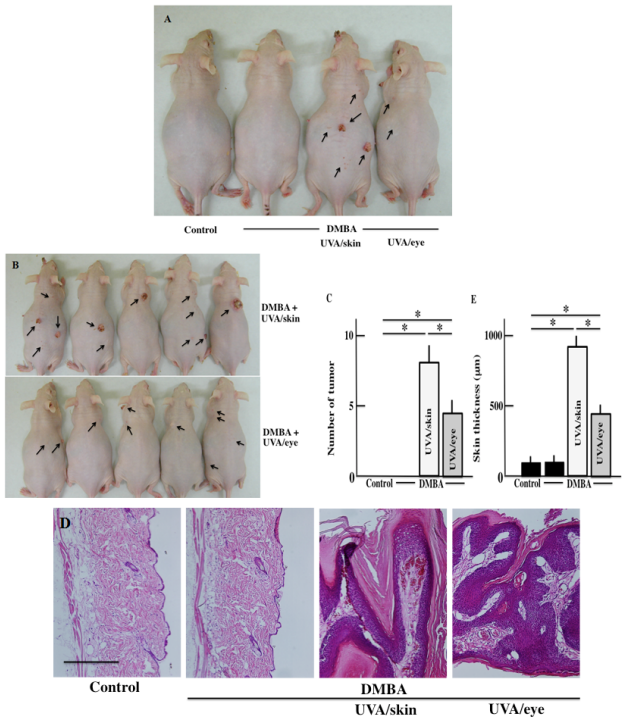

Figure 1: Effects of UVA irradiation in the eyes on non-melanoma skin cancer. The number of the tumors is shown (A,B,C). Histological analysis of skin sections has been performed (D,E). Skin samples were extracted after the final irradiation. Scale bar=100 μm. Values represent the means ± SD derived from 6 animals. *P<0.05.

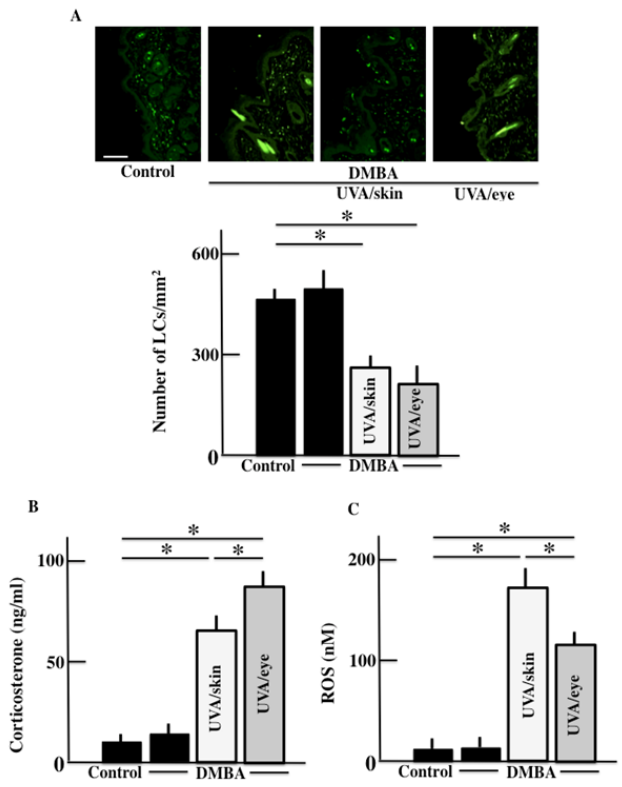

Figure 2: Effects of UVA eye irradiation on the plasma levels of reactive oxygen species (ROS) (A) and corticosterone (B), and on skin Langerhans cells (LCs) (C). The plasma and skin samples were extracted after the final irradiation. Scale bar=100 μm. Values represent the means ± SD derived from 6 animals. *P<0.05.

After collecting data on tumors (mean number of tumors per mouse) on the final day of examination, we extracted blood and skin samples under anesthesia. Skin specimens were fixed in phosphate-buffered paraformaldehyde (4%), embedded in frozen Tissue Tek, OCT compound (Sakura Finetek, Tokyo, Japan), and cut into 5-mm-thick sections, which were stained with haematoxylin-eosin (HE) in accordance with the established procedures for the histological analysis of the skin. The number of Langerhans cells (LCs) were evaluated immunohistochemically under a fluorescence microscope, as described previously [4,5]. The blood samples were fractionated. Plasma corticosterone and reactive oxygen species (ROS) levels were determined using commercial kits (corticosterone: AssayPro, St. Charles, MO, USA; ROS: Cell Biolabs, Inc., San Diego, CA, USA) in accordance with the manufacturer's instructions.

Results

Localized UVA irradiation of either eye or dorsal skin after initiation induced non-melanoma skin cancer. Upon skin cancer induction, the UVA skin-irradiated mice were more remarkable than the eye irradiated mice (Figure 1). Thereafter, we enumerated the LCs and quantified corticosterone levels to assess the extent of immunosuppression, thereby reinforcing cancer induction. The number of LCs decreased owing to either eye or skin irradiation (Figure 2A); however, there were no differences between the two groups. Plasma corticosterone levels increased owing to either eye or skin irradiation (Figure 2B), the eye-irradiated group displaying higher levels than the skin-irradiated group. Furthermore, upon eye or skin irradiation, DNA-damaging ROS levels were higher among skin-irradiated mice than among eye-irradiated mice, both displaying higher ROS levels than those among non-irradiated mice (Figure 2C).

Discussion

Skin irradiation generated free radicals and caused skin damage [6]. On DMBA treatment, these radicals further enhanced the carcinogenic function of DMBA [7]. In this study, the increase in blood ROS levels was observed not only in the skin-irradiated mice but also in the eye-irradiated mice, thereby indicating the possibility of promoting tumorigenesis. However, levels of UVA-induced ROS generation *via* eye irradiation were smaller than those after skin irradiation. Therefore, skin cancer induction was believed to be weak. Furthermore, owing to the important role of immunosuppression in skin cancer progression, although the number of LCs decreased upon UVA irradiation, there were no differences between skin and eye-irradiated groups. However, regarding blood levels of corticosterone, which supports immunosuppression, were higher in eye than in skin-irradiated mice. Hence, upon skin irradiation, adrenocorticotropic hormone (ACTH) is secreted from the proopiomelanocortin (POMC) system in the skin, which in turn stimulates corticosterone secretion; however, it has been reported previously that eye irradiation induces higher levels of ACTH from the pituitary gland in the POMC system [5]. These finding suggest that upon eye irradiation, ROS levels may increase slightly, thereby serving as a promoter; however, this may not be adequate for skin carcinogenesis. Moreover, immunosuppression had strong effects and was considered to readily promote skin cancer.

Our results indicate that skin cancer *via* a DMBA initiator was induced by UVA irradiation in the eyes. Furthermore, the increase in ROS serves as a trigger, and the increase in corticosterone resulted in immunosuppression and was considered to have caused skin cancer. In humans, lower levels of UVA approach the retina than those in mice. However, levels of UV radiation approaching the surface of the earth have increased in recent years. Furthermore, UV radiations are diffusely reflected from environmental alterations, and the amount of UV irradiation in the eyes has increased. These findings suggest that UV-exposed eyes may promote the genesis of skin cancer in humans. Future studies are required to elucidate the detailed mechanism underlying the onset of skin cancer due to UV irradiation in the eyes.

Acknowledgement

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Conflict of Interest

There are no conflicts of interest to declare.

References

1. Moan J, Grigalavicius M, Baturaite Z, Dahlback A, Juzeniene A (2015) The relationship between UV exposure and incidence of skin cancer. Photodermatol Photoimmunol Photomed 31: 26-35.

2. Reiners JJ Jr, Nesnow S, Slaga TJ (1984) Murine susceptibility to two-stage skin carcinogenesis is influenced by the agent used for promotion. Carcinogenesis 5: 301-307.
3. Fisher SM, Conti CJ, Viner J, Aldaz CM, Lubet RA (2003) Celecoxib and difluoromethylornithine in combination have strong therapeutic activity against UV-induced skin tumors in mice. Carcinogenesis 24: 945-952.
4. Yokoyama S, Hiramoto K, Koyama M, Ooi K (2014) Skin disruption is associated with indomethacin-induced small intestine injury in mice. Exp Dermatol 23: 659-663.
5. Hiramoto K, Jikumaru M, Yamate Y, Sato EF, Inoue M (2009) Ultraviolet A irradiation of the eye induces immunomodulation of skin and intestine in mice *via* hypothalmo-pituitary-adrenal pathways. Arch Dermatol Res 301: 239-244.
6. Halliday GM, Byrne SN, Kuchel JM, Poon TS, Barnetson RS (2004) The suppression of immunity by ultraviolet irradiation: UVA, nitric oxide and RNA damages. Photochem Photobiol Sci 3: 736-740.
7. Abel EL, Angel JM, Kiguchi K, DiGiovanni J (2009) Multi-stage chemical carcinogenesis in mouse skin: fundamentals and applications. Nat Protoc 4: 1350-1362.