The Role of Melanin in Skin Cancer

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ABSTRACT: Low melanin level in white skin results in many genetic alterations that activate oncogenes to form metastatic melanomas because of interaction with ultraviolet rays. These melanomas are uncommon, but they are dangerous and spread rapidly in the individual's body. Individuals with fair, freckled skin; a weak immune system; or have a personal or family history of melanoma are at high risk to have melanoma. There are different stages of melanomas. All have some treatments, but to achieve more efficient treatment, clinical trials are being done. Some of the treatments involve immunotherapy, radiotherapy, surgeries, and sentinel lymph node biopsy.

KEY WORDS: oncogenes, UV rays, melanoma, immunotherapy, sentinel lymph node biopsy

I. INTRODUCTION

Melanin is a pigment found in our body to keep us safe from many types of environmental stresses that includes reactive oxygen species and different types of solar ultraviolet radiation. These environmental stresses interact with different tissues of our body, which in turn disturbs many pathways and can increase or decrease levels of various hormones. Among these hormones, melanin is the one that is produced by the pituitary glands in cells known as melanocytes. These cells activate genes to encode RNA required for melanin synthesis. RNA encodes an enzyme for melanin production and the amino acid tyrosine. The enzyme and amino acid are taken up by some vesicles or sac-like structures known as melanosomes where melanin is produced.[1]

A. Melanin Characterization

Melanocytes prevail in many types of cells found in the eyes, epidermis, hair, oral epithelium, and elsewhere. In humans, tyrosine is enzymatically broken down into two categories of melanin.[2] These types include eumelanin and the pheomelanin (Fig. 1).

Melanin is a hormone that keeps our skin safe from the damage caused by ultraviolet rays from the sun.

B. Skin Pigmentation

Melanin gives color to our skin and produces two types of pigments: eumelanin, which is the primary type; and pheomelanin. The dark and long-lasting pigmentation results from eumelanin because it is insoluble. Pheomelanin gives a fair color to the skin. It is soluble and persists for only a short period. Eumelanin is the better shield against ultraviolet radiations, which is the reason that people who have pheomelanin in their skin are more susceptible to sunburn.[3]

Skin pigmentation also depends on the person's genetic makeup, which they inherit from their parents. Regardless of inheritance, genes producing melanin may be more or less expressed. Another means of producing melanin at a high or low level is the response to sunlight exposure, which enhances melanin production and darkens the skin. This type of melanin expression is only to protect our own skin cells from damage caused by sunrays. Another thing that may influence skin color is where the individual lives. If an individual lives where exposure to sunrays is maximum, then the pigmentation level of skin is high, and vice versa.[4]

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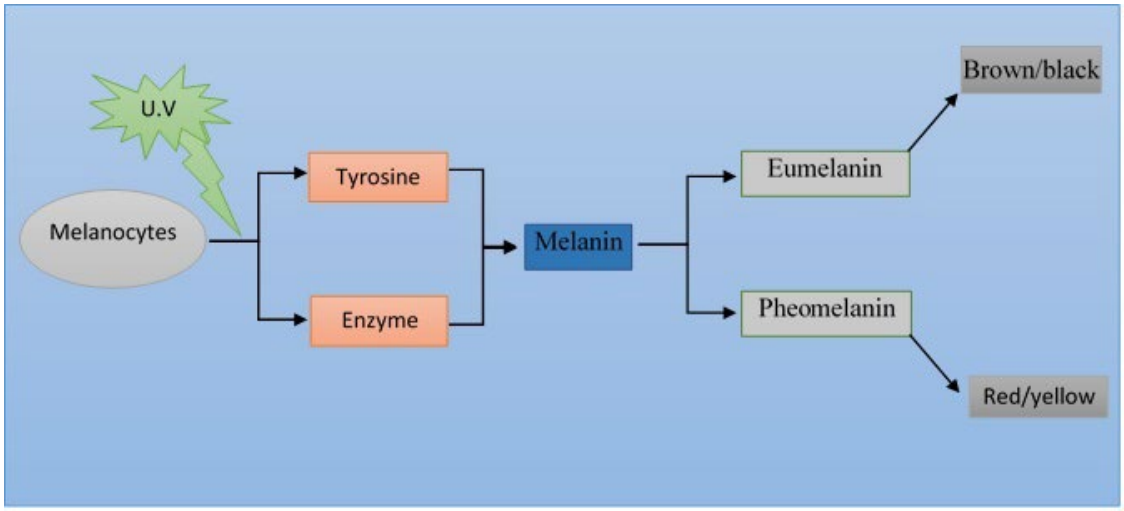

FIG. 1: Melanin production and characterization

1. The Melanin Shielding Effect against Sunlight Screening

Previous studies indicate that in addition to providing skin pigmentation, melanin protects us by screening out UV rays. According to the data collected with a survey of people with fairer skin, they are 70 times more likely to develop skin cancer than individuals with darker skin.[5] The melanin in persons with tanned skin screens out sunrays and allows only a low amount of UV rays to pass into the epidermis. Similar protection is not provided in individuals with light colored skin.

If the sun protection factor (SPF) level is 2, it means the effect of shielding by melanin increases twice against sunrays. Among individuals with white skin, the penetration level of ultraviolet B (UVB) is up to 24%; however, among individuals with darker skin, only 7.4% of ultraviolet B (UVB) rays can penetrate.[6] Similarly, the ultraviolet A (UVA) penetration level is 17.5% among individuals with dark skin, and 55% among individuals with light skin.[4]

2. Detrimental Fallouts of Melanin

Despite the fact that protection against UV rays is provided by melanin, and melanin saves us from sunburn, melanin also has some detrimental side effects.[7] Melanin can produce reactive oxygen species (ROS), such as superoxide anions or hydrogen peroxide. In skin, UV rays and ROS interact and cause ssDNA gaps inside the cells, which causes DNA mutations in some cells of the body, which imparts some carcinogenic effects. Pheomelanin is more influenced by these damaging effects. It can release histamine in excessive amounts and can result in erythema or edema, or it can cause cell death.[8]

Cancer risk can be related to the type of skin a person has. Among individuals with dark skin, the risk of cancer is much lower than that in individuals with light skin because of excessive melanin production. From skin cancers such as melanoma, the approximate death rate was 9730 in 2017, and the rate of incidence of melanoma increased from 2% to 3% in every year from 2004 to 2013. Among all types of skin cancer found in children, 6% of cases are from melanoma.[9]

II. SKIN CANCER

Skin cancer is the uncontrolled division of cells of the epidermis, which may result in a malignant formation. There are three basic forms of skin cancers, which include basal cell carcinoma, squamous cell carcinoma, and melanoma. Basal cell carcinomas are

associated with either the epidermal basal cell layer stem cells or hair follicles projected area.[10] Both the basal cell and squamous cell carcinomas result from genetic mutation or alterations (Fig. 2).[1]

A. Melanoma Skin Cancer

Inside cells producing melanin, the melanocytes, because of an abnormal level of changes, develop into melanoma. There are two main types of melanoma. One is cutaneous and the other one is malignant melanoma. In some melanocytes, instead of tumor development, melanin is produced in very low concentration. We detect those melanomas by their color, which are black or brown. These tumors can develop on various areas, including the chest, back, neck, legs, and face, but the most common sites are the neck and the face. Melanomas are less common but more deadly and have a greater dispersal rate

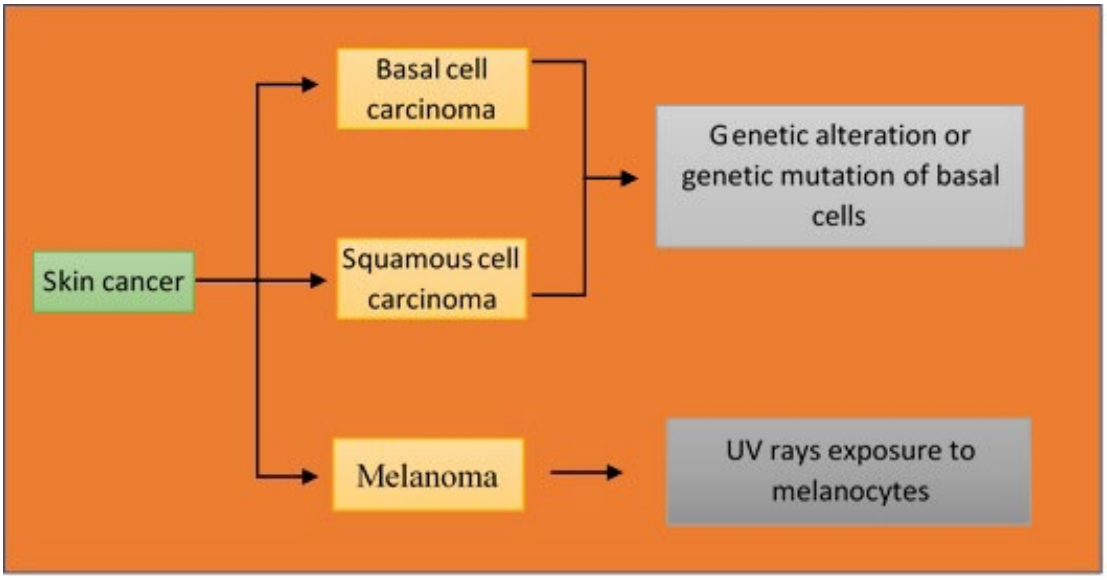

FIG. 2: Skin cells carcinoma characterization

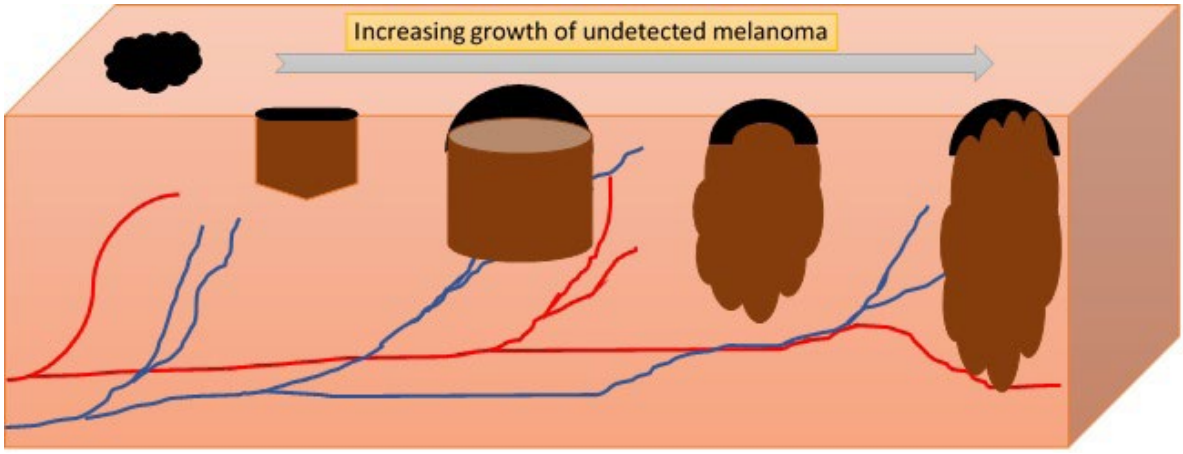

FIG. 3: Melanoma formation

than other two carcinomas (Fig. 3).

B. The Epidemiological Overview of Melanoma

According to yearly epidemiological surveys, the incidence of new occurrences of melanoma worldwide is estimated to be 132,000.[11] In Caucasians, the rate of incidence of melanoma is greater than that of African Americans and Hispanics.[6] According to the World Health Organization (WHO), the yearly death rate due to malignant skin cancer is estimated to be 65,161 worldwide. Among them, only 3% of melanoma cases occur in the United States. In the United States in 2009, among 121,840 new melanoma cases, about one died every hour, with the total death toll of 8650, as recorded by the American Academy of Dermatology.[11] The death rate has been increasing yearly in United States. Because of this alarming increase in the rate of incidence of skin cancer, it has become a big public health issue, and the main cause is exposure to UV rays.

C. The Melanoma Pathological Process Mechanism

When UV rays come in contact with the melanocytes and interact with some susceptible genes, which includes BRAF and CDK4. This results in incremental genetic mutations among melanocytes, through which oncogenes are expressed, which deactivates the suppressor genes of a tumor and damages the DNA repair. All of these processes cause metastasis formation, ultimately resulting in carcinoma of skin cells.[12] A brief description of these events is given in Fig. 4.

D. Hazardous Aspects of Melanoma

In different conditions, the high melanoma level

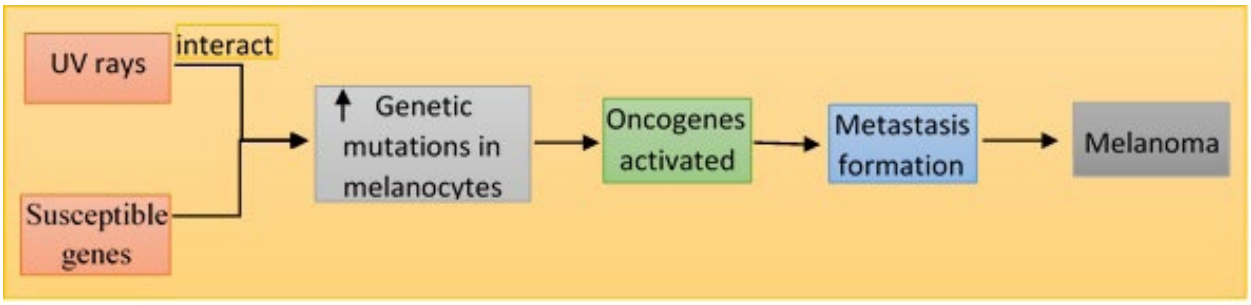

FIG. 4: Melanoma pathogenesis pathway

TABLE 1: Melanoma level in accordance with hazardous aspects

Hazardous aspect of melanoma	Level of melanoma
Light hair, fair and freckling skin	High level
Family history of melanoma	High level
Personal history of skin cancers	High level
Weak immune system (e.g., during organ transplantation and HIV infected individuals)	High level
Aged individuals	High level
Gender (i.e., male individuals) • Before 50s • After 50s	High level • High in women • High in men
Xeroderma pigmentosum (XP) patients	High level

responds differently. Some of the hazardous aspects of melanoma are listed in Table 1.[13-16]

E. Melanoma Phases with Treatments

The groups and stages of melanoma tumors are described by a system of letters and roman numerals, which includes T, M, and N groups, and 0, I, II, III, IV stages, which are further subdivided. These stages are determined on the basis of some criteria such as dispersion level of melanoma. There are also some treatments discovered according to each stage (Table 2).[17–19]

For all these stages, clinical trials are ongoing to find treatments to cure melanomas. The hard one melanomas are of stage IV.

Previously, different diseases have been managed by increasing the drug delivery to the target site by the use of polymers or nanotechnology; synthesis of new drugs, either by the use of proteomics, synthesis from lactic acid bacteria, or isolation from marine microorganisms; or the use of advanced therapeutic techniques.[20-36] Currently, however, the trend is shifting to the use of natural products or extracts to control the diseases.[37-56] Cancers including melanoma will be completely manageable in the near future.[57-76]

III. CONCLUSION

UV rays play the most damaging role in causing skin cancers and mainly the melanoma. Melanin protects our skin from damage caused by UV rays if excessively exposed to the sun. Among individuals with lighter skin who have low levels of melanin, UV radiation may lead to various genetic mutations resulting in melanoma formation in the skin, eyes, and other tissues. To treat those melanomas, we have

TABLE 2: Melanoma stages and their treatment

Melanoma stages	Description of melanoma stages	Treatments
Stage 0	Epidermal melanoma, no dispersal in deep layers	Surgery, imiquimod cream, or radiation therapy
Stage I • IA • IB	• < 1 mm thick melanoma, nonulcerated, not in distant organs and lymph nodes • < 1 mm thick melanoma, nonulcerated/ ulcerated, not in distant organs and lymph nodes	Sentinel lymph node biopsy or surgery
Stage II • IIA • IIB • IIC	• Thickness of melanoma is 1.01-2.0 mm • Thickness of melanoma is 2.01-4.0 mm • Melanoma thickness is > 4.0 mm, ulcerated	Adjuvant therapy, surgery, or sentinel lymph node biopsy
Stage III • IIIA • IIIB • IIIC	• No apart dispersal, not ulcerated, found in lymph nodes at a small level • No apart dispersal, ulcerated or not ulcerated, found in lymph nodes at small level or at large level • No apart dispersal, ulcerated, found in lymph nodes at small level, dispersal up to nearby skin areas	Surgical treatment, chemotherapy, radiotherapy, immunotherapy, targeted therapy
Stage IV	• Dispersal in lymph nodes and nearby organs or distant areas, thick melanoma, dispersed in lymph nodes	Surgical treatment, chemotherapy, radiotherapy, immunotherapy, targeted therapy

to reduce or curtail destructive outcomes from UV ray exposure, and we have to continue educating susceptible patients. We should develop techniques to increase melanin level among individuals who have melanomas and to improve diagnostics.

We should not limit ourselves to education of patients. Instead, we should educate individuals at the public level via different ways. By absolute education, people may be aware of UV exposure and its consequences, and we can minimize the incidence of melanoma to some extent.

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