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ROLE OF MICROBIOME AND SIGNAL TRANSDUCTION THERAPY IN COMBATING MELANOMA

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Abstract:
Skin cancer is the most common malignancy in the United States and the whole world. It represents a major burden to public health and needs a special attention. Major steps to treat skin cancer had been taken and a combination therapy had been sought and it is quite promising. Melanoma is an example of a dual-mutation tumorigenesis and at least two mutations are required before its development. This fact is the cornerstone of signal transduction combination therapy which blocks the pathways involved in carcinogenesis. A better understanding of these pathways and the timing of genetic mutations will open the door widely to new treatment strategies and help in controlling this disease. On the other hand, skin microbiome represents a revolutionary step in the treatment and prevention of skin cancer. A special strain of Staphylococcus epidermidis produces 6-N-hydroxypurineamine, which is found to inhibit the proliferation of rapidly dividing cancer cells and suppress UV-induced skin tumor in mice. Accordingly, the presence of this strain on the surface of human skin could be protective against neoplasia. It is well understood that cutaneous HPV can cause non-melanoma skin cancers and HPV vaccine is used to protect against such cancers. In the future, 6-HAP-producing Staphylococcus epidermidis could be isolated and used in manufacturing a vaccine against melanoma. Similarly, using the genes that code for 6-HAP in these bacteria and incorporating these genes in the production of sunscreens will hopefully be the next innovative step in controlling this deadly disease.

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INTRODUCTION:

Skin cancer is the most common malignancy in the United States and the whole world. It represents a major burden to public health and needs a special attention. Major steps to treat skin cancer had been taken and a combination therapy had been sought and it is quite promising. Melanoma is an example of a dual-mutation tumorigenesis and at least two mutations are required before its development. This fact is the cornerstone of signal transduction combination therapy which blocks the pathways involved in carcinogenesis. A better understanding of these pathways and the timing of genetic mutations will open the door widely to new treatment strategies and help in controlling this disease. The cutaneous microbiome is another interesting piece of the jigsaw puzzle. The role of commensal microorganism in development and may be risk mitigation of skin cancer, is now under extensive research.

Biology and Descriptive Epidemiology:

Skin is the largest and fastest-growing organ in the human body. (1) Anatomically, it is composed of three layers: the outer epidermis, the inner dermis, and a layer of subcutaneous tissue. (2). Melanocytes are specialized pigment-producing cells identified at the dermo-epidermal or in the superficial dermis (3). Also, they have been found in the inner ear, nervous system and the heart. (4, 5). Malignant melanoma is an aggressive and fatal form of skin cancer that originates in melanocytes. It is the third most common skin cancer in the United States. (6) The incidence rate of skin cancers is 3-4 times higher than HIV infection. (8, 9).

Each year in the US, nearly 5 million people (~1.5% of the population) are treated for all skin cancers combined, including non-melanoma skin cancers, with an annual cost estimated at $ 8.1

billion. (7) Invasive melanoma accounts for about 1% of all skin cancer cases. An estimated 91,270 new cases of melanoma will be diagnosed in the US in 2018. (10) This disease is most common in Non-Hispanic White with an annual incidence rate of 26/100000, compared to 4/100000 in Hispanic and 1/100000 in African American. Gender and age play a big role in the incidence of melanoma. Before age 50, the incidence rate is lower in men than in women. By the age 65, rates in men are twice those in women, and by age 80, they are triple. (10)

Hispanics are typically diagnosed at later disease stages and suffer higher morbidity and mortality. They have the highest uninsured rate in the US. (24) Additionally, there is a wrong assumption among this population that they are immune from getting skin cancer due to their darker skin trait. They tend to use less precautionary measures to protect against the development of this tragic disease. (23) Studies show that Hispanics have less melanoma awareness than their non-Hispanic white counterparts and they are less likely adhering to screening guidelines or performing skin self or physician-assisted examination (25,26)

Hispanics work in outdoor occupations like landscaping, construction, and transportation, all of which are linked with significant sun and chemical exposure. A high percentage of Hispanic workers reported never wearing sunscreen and significant associations had been found between melanoma and chemicals used in agriculture. (27, 28)

Etiology:

There are two major etiological factors that correlate with an increased risk of melanoma and they are important from the public health perspective. Environmental factor, which is represented by chronic sun exposure or UV light. UV radiation can damage DNA and lead to several mutations in the genes involved in the development of the skin cancer. UVB part of sunlight is thought to be responsible for the development of skin carcinogenesis. Variable disruptions of the oncogenic, tumor-suppressive, and cell-cycle control signaling pathways occur during this process. Despite that UV radiation exposure is recognized as a major environmental risk factor for melanoma, many epidemiological studies failed to show robust association and it is unclear which spectrum of UVR contributes the most to skin cancer development. (14)

The relationship between sun exposure and risk of melanoma is a bit complex. Skin tone is another non-modifiable parameter which interacts with sun exposure. Individuals with sun-sensitive skin type are at increased risk of melanoma and they should avoid sunburn and sunbathing while in those with non-sun-sensitive skin type, the risk is lower (11)

Genetic factors also play a large role in the development of melanoma. More than half of the risk of melanoma is caused by inherited genes. (13) CDKN2A, a cyclin-dependent kinase inhibitor 2A, which is located on chromosome 9p21, acts as a security guard and provides a mechanism for holding damaged cells at the G1/S checkpoint to permit DNA repair before cellular replication. Loss of its function is a critical step in carcinogenesis. Mutations in CDKN2A/P16 accounts for a large percentage of all familial melanoma. (11, 12)

Prevention and Control of Melanoma:
To prevent the occurrence of Melanoma, certain measures should be implied. Intense intermittent exposure to UVR as well as Indoor tanning bed should be avoided, especially during adolescence, as it is associated with an increased risk of early-onset melanoma. (11, 16). Regular use of sunscreen with SPF above or equal to 15 has been shown to reduce melanoma incidence significantly. (17,18). Genetic testing for CDKN2A mutation, utilization of full body photography and dermoscopy to observe lesions in a high-risk population and teaching them to perform skin self-examination technique monthly are innovative preventive measures. (19)

Thirteen US states passed legislation for sunscreen use (i.e. carry and self-apply) among schools. The remaining states should adopt the same policy to achieve cancer-free status among young individuals. Research conducted by a CDC-funded prevention and research center continues to advance our understanding of indoor tanning behaviors. USPSTF released new recommendation for behavioral counseling on skin cancer in March 2018. It recommends counseling young adults, adolescents, children, and parents of young children about minimizing exposure to UVR for persons aged 6 months- 24 years with fair skin type to reduce their risk of skin cancer. Existing evidence of counseling all adults older than 24 years is small. In December 2015, the FDA proposed a nation-wide rule to restrict tanning bed use to adult aged 18 years or older and require that they sign a risk acknowledgment certification before use. Skin cancer prevention policies in schools and outdoor activities restriction during midday hours should be followed to reduce the incidence of sunburns and the associated risk of melanoma (15)

Treatment Strategies for Melanoma:
Surgical excision with safety margins remains the primary modality for treating melanoma. The use of IFN Alpha 2b as an adjuvant therapy, for patients with melanoma who have undergone a complete surgical resection, improves relapse-free survival and overall survival. (21)

Surgically unapproachable Melanoma can be treated by two families of immunotherapeutic agents. Checkpoint inhibitors, like pembrolizumab, nivolumab, and ipilimumab, and signal transduction inhibitors, which are subdivided into two main groups; BRAF inhibitors like Vemurafenib, Dabrafenib and MEK inhibitors like Trametinib, cobimetinib.

Combination of BRAF and MEK inhibitors have been approved by FDA and will become the standard of care of BRAF-mutated melanoma. BRAF gene, which is also called BRAF proto-oncogene or serine/threonine kinase, codes for a protein that helps transmit signals from outside of the cell to the cell's nucleus. This protein is a part of a signaling pathway called RAF-Mitogen-Activated Protein Kinase pathway, RAF-MAPK pathway. The latter controls many cell functions like cell proliferation, migration, differentiation, and self-destruction. Mutation of this gene will eventually lead to carcinogenesis. This is a good example of a two-mutation model of tumorigenesis. UV radiation from the sun or other environmental risk factors causes a somatic V600E mutation occurs during a person's lifetime. This mutation often leads only to the formation of a noncancerous mole. At least one extra mutation is necessary for the development of melanoma. (29) BRAF inhibitor monotherapy provides limited response due to the emergence of resistance. Combination of a MEK and BRAF inhibitor will help in overcoming resistance issues and improve treatment outcome by reducing local toxicity. Identification of individuals with the BRAFV600E mutation will be a helpful screening tool to utilize the BRAF/MEK inhibitor combination therapy. (30)

On the other hand, skin microbiome represents a revolutionary step in the treatment and prevention of skin cancer. A special strain of *Staphylococcus epidermidis* produces 6-N-hydroxypurineamine, which is found to inhibit the proliferation of rapidly dividing cancer cells and suppress UV-induced skin tumor in mice. (31) Accordingly, the presence of this strain on the surface of human skin could be protective against neoplasia. It is well understood that cutaneous HPV can cause non-melanoma skin cancers and HPV vaccine is used to protect against such cancers. (32) In the future, 6-HAP-producing *Staphylococcus epidermidis* could be isolated and used in manufacturing a vaccine against melanoma. Similarly, using the genes that code for 6-HAP in these bacteria and incorporating these genes in the production of sunscreens will hopefully be the next innovative step in controlling this deadly disease.

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