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Introduction to Melanoma: Risks, Development, and Treatment

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ABSTRACT

This paper provides a general introductory overview to malignant melanoma, one of the most common, yet deadly skin cancers in the world. The two main categories of melanoma, cutaneous and non-cutaneous, have differences in affected tissues, risk factors, and driving mutations. The carcinogenesis of melanoma is driven by pathogenic dysregulation in the MAPK pathway, p53 protein, and cell cycle checkpoints. There exist four main treatment approaches up to date: surgical resection, chemotherapy, targeted therapy and immunotherapy. Although recent advancements in immunotherapies have improved treatment options immensely, additional research is needed to develop more effective strategies to lower the mortality rate further.

Introduction

Melanoma is a malignant cancer that affects epidermal melanocytes (Raimondi et al, 2020). Since melanoma is a type of skin cancer, its development can be seen with the unaided eye. Visual characteristics of melanoma include dark enlarged moles, swelling, inflammation, and dry flaky skin patches. The United States had a yearly melanoma incidence of 21.5/100,000 and a death rate of 2.2/100,000 from 2015-2019 (NCI SEER). Globally, melanoma affected 3.1/100,000 people and claimed 0.63/100,000 lives in 2018 (Raimondi et al, 2020). Australia has the highest incidence of melanoma in the world with 36.6 cases per 100,000 individuals annually (WCRFI). This is likely the result of prolonged exposure to extremely high UV levels (frequent summer UV index of 12–14) in Australia (Cancer Council Australia), which is directly correlated to melanoma incidence rates.

Risk Factors

Melanoma cases are categorized as cutaneous or non-cutaneous depending on location and the type of tissue being affected. Cutaneous melanoma develops in the melanocyte cells of the skin, while non-cutaneous melanoma usually develops in mucosal or uveal tissue (Vergara et al, 2022). Cutaneous melanoma risk factors fall into two major categories: UV exposure factors and host factors.

UV exposure patterns can be sporadic or continuous. Some examples include regular tanning under the sun, not using UV radiation (UVR) protection, and frequent tanning bed use. Since UVR is carcinogenic, any exposure to it increases one's likelihood of developing melanoma in the future. UVA, which makes up ~95% of the sun's UV rays, inflicts harm on the skin through the introduction of reactive oxygen species (ROS). If abundant, ROS indirectly alters the genetic makeup of cells. Though UVB only makes up <5% of UVR, it acts as a "potent mutagen that directly alters nucleotide structure in DNA" (Nasti & Timares, 2015). Due to the high risk of tumorigenic induction by artificial UVA and UVB emissions, tanning beds were classified as a group 1 carcinogen in 2009 (Mogensen & Jemec, 2010).

Examples of host factors include the amount of eumelanin and pheomelanin in the skin, the propensity for moles to form, and one's genetic make-up. For example, individuals with light skin (less melanin) are seventy times more likely to develop melanoma in their lifetime compared to their darker-skinned counterparts with higher melanin

levels (Nasti & Timares, 2015). Additionally, it has been discovered that the presence of the amino acid L-tyrosine causes the melanocytes in lighter skin to produce more pheomelanin (Nasti & Timares, 2015), in which glutathione stores are more susceptible to damage due to the usage of glutathione to deliver cytosine during the synthesis of pheomelanin. The impairment in glutathione stores can alter the genome in melanocyte cells and lead to "genetic instability" (Nasti & Timares, 2015). When host factors that lead to genetic instability in the melanocytes of an individual are combined with external UVR risk factors, the likelihood of melanogenesis resulting from further genome discrepancies increases exponentially.

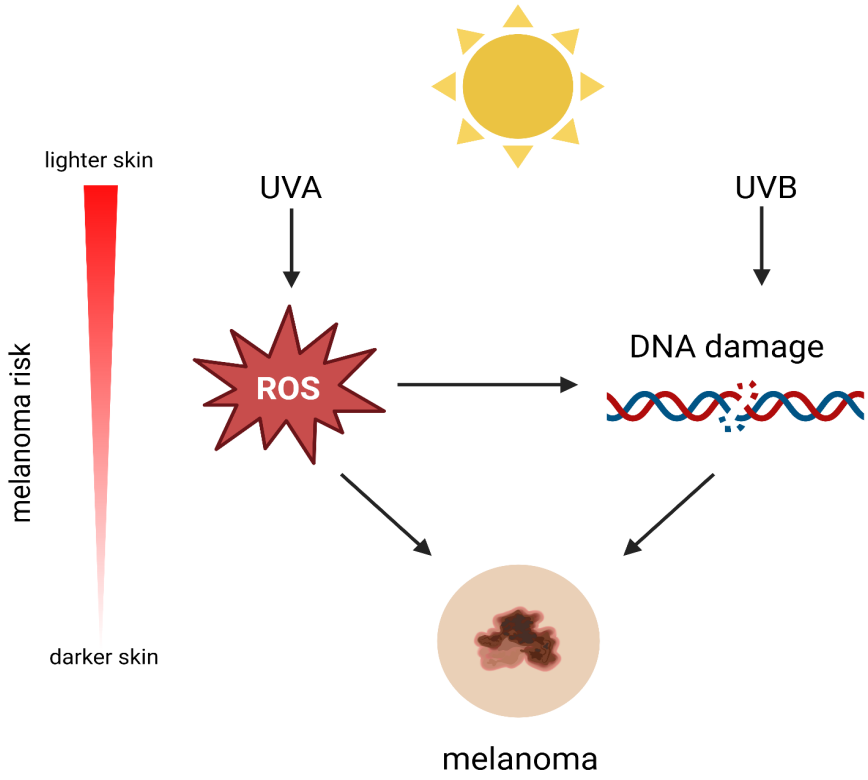

Figure 1. Environmental and genetic risk factors of melanoma.

Cutaneous vs. Non-Cutaneous

All melanoma tumors have the appearance of dark pigmented spots on tissue. In the melanocytes of both cutaneous and non-cutaneous melanoma tumors, β1-6 branched oligosaccharides are found. This carbohydrate processing structure is not found in healthy melanocytes (Lazova & Pawelek, 2009). However, UVR is not as strong of a causative mutagen in the development of non-cutaneous melanoma compared to the development of cutaneous melanoma. Although non-cutaneous melanoma is a much rarer oncological phenomenon, its response to immunotherapy is far less promising than that of cutaneous melanoma (Vergara et al, 2022). In non-cutaneous melanoma, tumors in regions of the body not exposed to UVR generally bear fewer mutations than tumors exposed to UVR. One key difference between cutaneous and non-cutaneous melanoma is their variation in driver mutations. In cutaneous melanoma, driving mutations in the V-Raf murine sarcoma viral oncogene homolog B1 (BRAF) and neuroblastoma RAS viral oncogene homolog (NRAS) oncogenes are very common and significantly correlate to the carcinogenesis of these tumors (Vergara et al, 2022). These mutations are heavily linked to UV exposure, which is the main cutaneous melanoma risk factor. However, there are six different conjunctival melanomas (non-cutaneous melanoma of eye tissue) that show

no evidence of BRAF or NRAS oncogenic mutations (Vergara et al, 2022). While cutaneous and non-cutaneous tumors are virtually identical in appearance, they differ in the body tissues being affected, as well as in risk factor correlation and driving mutations.

Carcinogenesis

The MAPK pathway is the most common pathway for the tumorigenesis of melanoma (Teixido et al, 2021). When a receptor tyrosine kinase (RTK) boosts the activity of the RAS guanosine triphosphatases (GTPase), the mitogen-activated protein kinase pathway (MAPK pathway) begins. The signal enters the nucleus through the phosphorylation cascade of RAF, MAP2K1, and extracellular signal-related kinase (ERK), where transcription begins and the cell cycle is activated (Teixido et al, 2021). Some mutations in BRAF such as a Valine residue at the 600 position, increases the kinase activity of BRAF, while the genetic mutation at the Glutamine 61 position of NRAS leads to abnormally unvarying activity in the KRAS gene (Teixido et al, 2021). Both are a result of constitutively MAPK-activated melanoma and further contribute to the unregulated mitogenesis of melanoma tumor cells.

All cancer cells go through the process of initiation in order to proliferate as a tumor. Before cells undergo mitosis, there are many cell cycle checkpoints that the cell has to pass in order to continue the process of dividing. The first major checkpoint is the G1/S checkpoint. At this point in the cell cycle, the parent cell will have higher levels of cyclin D and cyclin E, which activate cyclin-dependent kinases (CDK2, CDK4, and CDK6 enzymes). CDK activity can be regulated by a group of proteins, called CDK inhibitors (such as p16, p21, p27), which evaluate whether or not the cyclin levels in the cell are appropriate for mitosis to continue, as inaccurate levels of cyclin signal that the genome of the cell may be unstable and that significant mutational impairment may be present. The second major checkpoint is G2/M, which takes place during the G2 stage. CDK1 protein levels are responsible for determining whether or not a cell should be permitted to begin the process of mitosis. If not, the cell will enter G2 arrest and try to repair its chromosomes. In the case that the problem cannot be fixed, the cell initiates apoptosis to prevent genomic instability from multiplying (de Gooijer et al, 2017). This final checkpoint prior to entering mitosis is especially important because any parent cells with mutations significant to the oncogenesis of melanoma that were not detected during the checkpoints will be able to proliferate into daughter cells with identical genomes. One gene that is commonly mutated in proliferating tumor cells is the TP53 gene. If TP53 is mutated genetically or epigenetically to lose its function, its downstream CDK inhibitor protein will be downregulated. Therefore, the CDK proteins will be constitutively active and not function as a reliable evaluating source during cell cycle checkpoints (Morris et al, 2001). Somatic mutations to CDKN2A (the gene encoding p16) from melanoma can affect the checkpoint process of cell division. This prevents p53 regulation in the cell (Teixido et al, 2021).

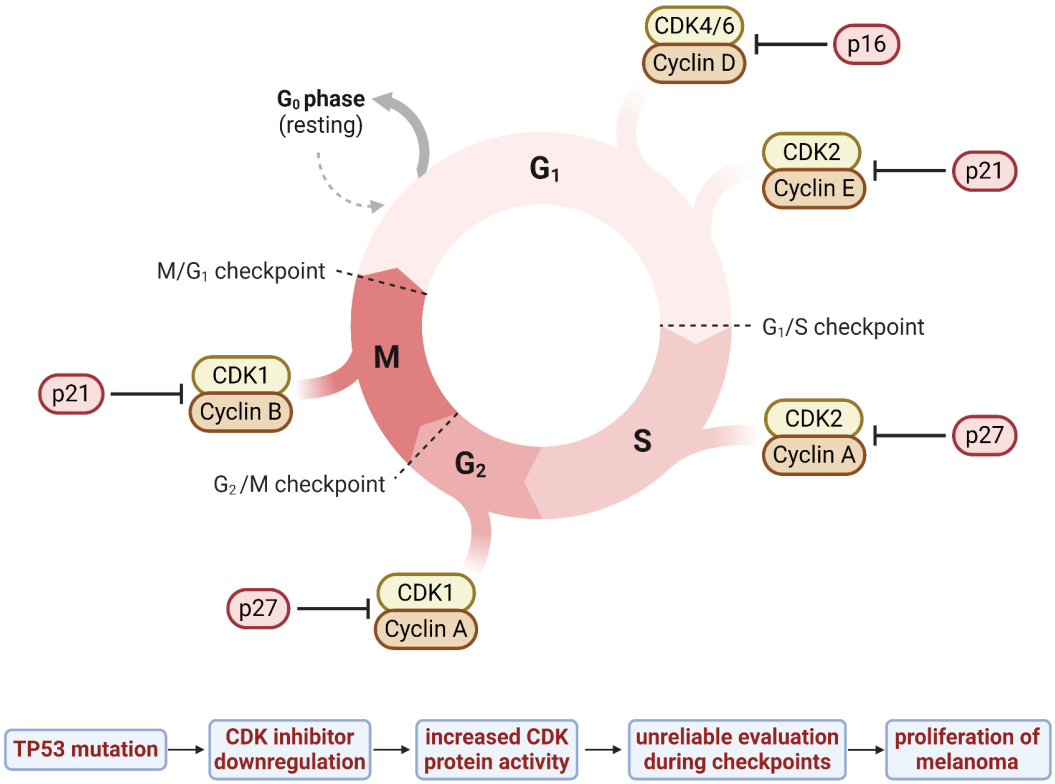

Figure 2. TP53 loss-of-function mutation resulting in abnormal CDK activity and proliferation of melanoma.

Treatment

There are four main types of melanoma treatment: surgical resection, chemotherapy, targeted therapy and immunotherapy. When surgical resection is performed, the tumor and some surrounding healthy skin are removed. In order for surgical resection to be considered a viable option, the melanoma has to be localized and cannot have metastasized to other areas of the body. Once melanoma has metastasized, survival rates decrease exponentially (Davis et al, 2019). At this point, chemotherapy, a drug designed to genetically damage cancer cells, is proposed as a treatment option. Despite having a one-year survival rate of just 27%, chemotherapy, specifically dacarbazine, was the only other melanoma treatment option available until very recently (Davis et al, 2019). In the past few years, targeted therapy and immunotherapies became available to melanoma patients with metastasized tumors. These therapies include vemurafenib and dabrafenib, small molecule drugs inhibiting mutant BRAF kinase activity while sparing wild type BRAF protein function, which enhances therapeutic window. BRAF mutations are extremely common, occurring in about 50% melanoma patients. Even though targeted therapies have a response rate of about 50%, resistance to the drug became common among those who used it (Davis et al, 2019). Immunotherapy, on the other hand, could offer cure to metastatic melanoma patients by aiding the immune system in finding and killing cancer cells.

Conclusion

Melanoma is a worldwide health concern that poses significant danger to the lives of many due to its high incidence and mortality rates. Many factors play key roles in the development of cutaneous melanoma, including UV exposure and host factors. However, non-cutaneous melanoma has different factors that increase one's susceptibility to the disease. Understanding the molecular pathways and genetic alterations involved in melanoma's carcinogenesis is vital

to providing opportunities for targeted therapies (although drug resistance poses a challenge to the efficacies of such treatments). Further research is needed to improve the overall understanding of melanoma and develop more effective treatment strategies.

Limitations

The contents of this review paper are restricted only to information publicly available at the time of submission and do not reflect future developments beyond the publication date.

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All figures generated on BioRender.

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