Melatonin as a Repurposed Drug for Melanoma Treatment

Subjects: Oncology

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Melanoma is the most aggressive type of skin cancer, with a greater risk of metastasis and a higher prevalence and mortality rate. This cancer type has been demonstrated to develop resistance to the known treatment options such as conventional therapeutic agents and targeted therapy that are being used as the standard of care. Drug repurposing has been explored as a potential alternative treatment strategy against disease pathophysiologies, including melanoma. To that end, multiple studies have suggested that melatonin produced by the pineal gland possesses anti-proliferative and oncostatic effects in experimental melanoma models. The anticarcinogenic activity of melatonin is attributed to its ability to target a variety of oncogenic signaling pathways, including the mitogen-activated protein kinase (MAPK) pathways which are involved in regulating the behavior of cancer cells, including cell survival and proliferation. Additionally, preclinical studies have demonstrated that melatonin in combination with chemotherapeutic agents exerts synergistic effects against melanoma.

Keywords: melatonin ; drug repurposing ; melanoma

1. Introduction

Melanoma is a malignant type of skin cancer that originates from melanocytes, a cell type that is essential for the melanin synthesis required for skin color [1][2][3][4]. The incidence of melanoma has been dramatically increasing worldwide over the last few decades [4][5]. Presently, the prevalence of developing melanoma is 1 in 63 people in the USA [5]. According to statistical estimates by the American Cancer Society, about 99,780 new melanomas (57,180 in men and 42,600 in women) will be diagnosed in 2022 in the USA.

Melanoma, due to its malignant nature, has a poor prognosis, is mainly present in patients with advanced or metastatic disease, and is highly aggressive when compared to other skin cancers such as squamous and basal cell carcinomas [1][2][3][4][5]. The common etiological factors include exposure to ultraviolet radiation, having fair complexions such as red or blond hair, blue or green eyes, and family history of melanoma [4][5][6][7][8]. Ultraviolet (UV) radiations are of three types, namely, UVA, UVB, and UVC, where UVA and UVB can reach and penetrate through the skin layers; however, UVC rays cannot penetrate the ozone layer [6][7]. UVB radiations are more prone to causing melanomas when compared to UVA due to the capacity of UVB to regulate the melanocortin 1 receptor (MC1R) expression, and melanocyte pigmentation. This leads to oxidative changes and endoplasmic reticulum (ER) stress downstream to MC1R, cyclic adenosine monophosphate (cAMP), and inhibition of phosphatidylinositol-3 kinase protein kinase B (PI3K/AKT) signaling [3][6]. This, in turn, alters the melanocyte-inducing transcription factor (MITF), which plays a pivotal role in the differentiation of melanocytes [6]. Alterations in MITF have been shown to cause the rapid proliferation of melanocytes, leading to melanogenesis [3][6][7][9].

2. Importance of BRAF Mutations in Melanoma

The cellular and biochemical changes that occur during the pathogenesis of melanoma serve as potential targets for therapeutic interference. For example, initial alterations in melanocytes would result in a benign nevus which remains non-cancerous and is controllable. However, overactivation of the growth regulating mechanisms, such as the mitogen-activated protein kinase (MAPK) signaling pathway, that help support the cell cycle in a homeostatic balance of growth, proliferation, and apoptosis has been shown to result in uncontrollable growth signals, triggered by a single mutation in the MAPK pathway, which leads to cancer [10][11].

Of importance, the v-raf murine sarcoma viral oncogene homolog B1 (BRAF) is a serine/threonine protein kinase that plays a critical role in RAS-RAF-MEK-ERK MAPK signaling. Importantly mutations in the BRAF kinase are the most prevalent driver mutations that lead to the MAPK pathway overactivation [10][11][12]. Within the MAPK pathway, RAF

belongs to the family of oncogenic serine-threonine protein kinases. Around half of all metastatic melanoma cases harbor BRAF mutations, particularly, valine (V) for glutamic acid (E) substitution at position 600 (V600E), which accounts for roughly 84.6 percent of all BRAF mutations [13][14]. The substitution of valine (V) for lysine (K) at position 600 (V600K) is a second prevalent amino acid change accounting for 7.7% of BRAF mutations [15][16][17]. While BRAF mutation alone may not contribute to the formation of melanoma, driver mutations in the tumor suppressor genes are frequently required for malignant melanoma progression [12][14][15]. Apart from these, KRAS, NRAS, and P13K/Akt/mTOR mutations also occur in 10% of melanoma cases [12].

3. Therapeutic Options for Melanoma

The therapeutic options for melanoma treatment depend upon tumor stages. Primarily, cutaneous melanoma in its early stages with localized lesions can be treated with surgical interventions which have higher recovery options with fewer adverse effects and better quality of life [18]. However, if melanoma progresses to highly aggressive or metastatic states, then treatment strategies vary from chemotherapy to cytokine-based therapies to targeted therapies and immune checkpoint receptor inhibitors [15][17][18]. In chemotherapy, some of the commonly used agents are dacarbazine, temozolomide, lomustine, and vinorelbine, whereas targeted therapy, which is currently considered the first-line treatment option for melanoma, includes BRAF inhibitors such as vemurafenib, dabrafenib, and cobimetinib [18][19].

The BRAF-targeted therapy is used either alone or in combination with the MEK inhibitors such as trametinib, and binimetinib, which are associated with improved survival rates and increased therapeutic effect in patients with BRAF-mutated melanomas [20][21][22]. Although targeted therapies are beneficial, often, tumor cells tend to develop resistance (within several months) to such approaches, resulting in a decreased clinical prognosis of the patients [21][22]. Moreover, such therapeutic options present other limitations, for example, targeted therapy-mediated high response rate is associated with overall short-term therapeutic benefits [23][24][25][26].

Immunotherapies include anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA-4, Ipilimumab), anti-programmed cell death protein 1 (anti-PD-1, nivolumab, and pembrolizumab), and anti-PD-ligand 1 (anti-PD-L1, atezolizumab). These therapies decrease tumor growth and metastasis and are used in combination with other therapeutic regimens, including targeted therapies [23][24][25]. Importantly, immune checkpoint inhibitors have been shown to result in overall higher survival benefits among patients; yet, they are associated with a lower response rate [26][27].

Notably, a few clinical trials reported increased doses of pharmacotherapy to patients, which was associated with adverse effects such as skin rash, keratoacanthoma, hyperkeratosis, headache, arthralgia, pyrexia, and atopic dermatitis, and 7% to 9% cases were shown to develop cardiac abnormalities that include decreased ejection fraction and interstitial lung diseases such as pneumonitis [28]. Therefore, due to these ongoing challenges associated with conventional therapies, including adverse side effects, various adjuvant therapies, including melatonin are being explored as repurposed drugs in cellular and preclinical models because of their anticancer properties in melanoma [29].

4. Melatonin as Drug Repurposing

Melatonin (N-acetyl-5-methoxytryptamine) is a chronobiological regulatory hormone produced at night by the pineal gland. It possesses various functions ranging from regulating circadian rhythms to antioxidant, anti-inflammatory, immunomodulatory, and anti-aging properties. Importantly, it also exerts cytoprotective effects in normal cells and triggers apoptotic signals in oncogenic cells [30][31][32][33][34][35][36][37][38]. As melatonin is lipophilic in nature, it can easily penetrate through the cellular membrane to protect intracellular structures such as DNA and mitochondria from oxidative stress induced by free radical generation. Melatonin, due to its pleiotropic actions, has provided the rationale to investigate its anti-proliferative and oncostatic effects and the underlying mechanisms in in vitro and in vivo experimental models of melanoma [31][37][39][40][41][42].

Melatonin is produced by the indole pathway from its precursor serotonin, and then it is metabolized into three different metabolites, 5-hydroxymelatonin, AFMK (N1-acetyl-N2-formyl-5-methoxykynuramine), and 5-methoxytryptamine by the indolic and kynuric pathways. Melatonin and its metabolites mediate their effects through MT1 and MT2 receptors present on the cell membrane [31].

These G-protein coupled receptors are conventionally considered monomers, but they also act as homodimers and heterodimers, which inhibit adenyl cyclase and cAMP. The absorption of linoleic acid is reduced when cAMP synthesis is reduced. The 15-lipoxygenase enzyme converts linoleic acid to 13-hydroxy octadecadienoic acid (13-HODE), which acts as a preliminary energy source for tumor signaling molecules and tumor development pathogenesis.

Importantly, recent evidence indicates that melatonin synthesis and metabolism can also affect tumor microenvironment. In a recent report, Lv and colleagues performed genomic analysis of the melatonergic system within the tumor microenvironment using RNA-seq data from The Cancer Genome Atlas (TCGA) of solid human tumors, including melanoma to determine their clinical relevance [43]. The data demonstrated that melatonin synthesis and its accumulation within the tumor microenvironment negatively correlated with tumor burden as well as mutational burden [43]. Overall, the studies indicated the clinical relevance of the melatonergic system as a promising prognosticator and potential indicator of immunotherapy response.

Melatonin's antiproliferative and oncostatic actions are thought to be due to its inhibition of linoleic acid absorption [35][44]. Melatonin also activates the apoptosis-targeting proteins p53 and p21. [33][34][35][38][45]. Apart from causing apoptosis, melatonin and its metabolites act as antioxidants forming a free radical scavenger cascade protecting tissues from oxidative damage. Specifically, melatonin protects the skin from UV damage by enhancing the expression of enzymes such as superoxide dismutase (SOD) and glutathione (GSH) peroxidase (GPx), which aid in skin cell protection [44].

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