Review

Mechanisms of Altered Immune Response in Skin Melanoma

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ABSTRACT: Melanoma, a deadly form of skin cancer, poses significant challenges to the host immune system, allowing tumor cells to evade immune surveillance and persist. This complex interplay between melanoma and the immune system involves a multitude of mechanisms that impair immune recognition and promote tumor progression. This review summarizes the intricate strategies employed by melanoma cells to evade the immune response, including defective immune recognition, immune checkpoint activation, and the role of regulatory T-cells, myeloid-derived suppressor cells, and exosomes in suppressing anti-tumor immunity. Additionally, we discuss potential therapeutic targets aimed at reversing immune evasion in melanoma, highlighting the importance of understanding these mechanisms for developing more effective immunotherapies. Improved insights into the interactions between melanoma and the immune system will aid in the development of novel treatment strategies to enhance anti-tumor immune responses and improve patient outcomes.

KEYWORDS: *Melanoma, skin cancer, immune response.*

Introduction

The skin is the body's largest organ, constantly exposed to various mechanical, thermal, and chemical aggressors.

While any of these factors can damage the skin's integrity, UVR have been linked to premalignant and malignant skin lesions by triggering a cascade of biological effects induced by the presence of photons [1,2].

This is because the chromophores typically found in human skin, such as melanin, capture UVR-photon energy through a process known as light absorption, causing their electrons to become excited when exposed to light [1].

While the excitation is limited, the process is not harmful, and slight, short-lived inflammation is essential for skin repair, regeneration, and remodeling [3].

However, if the excitation lasts long enough, preventing the chromophore from returning to the basal state (reached by dissipating energy in the form of heat or photon emission), a pro-photooxidative state of the skin is reached, leading to the appearance of reactive oxygen species (ROS), chronic inflammatory signaling, and immunosuppression, resulting in tissue homeostasis alteration [4,5].

While the immune response to melanoma was considered essential in the treatment of the condition, the survival rates of patients diagnosed with metastatic melanoma remained stagnant as no real progress was made, especially for patients with metastatic progression [6].

However, the emergence of advanced molecular diagnostic methods has led to the identification of many genetic mutations, amplifications, and deletions that seem to play a crucial role in promoting tumor development and survival signaling [7].

This is crucial because melanoma cells are continually changing to adapt to host defenses [7].

In this brief communication, we will briefly review the main cellular and molecular mechanisms through which melanoma cells outsmart and evade the host immune response.

These mechanisms include sustaining proliferative signaling, inducing angiogenesis, evading growth suppressors to activate and sustain invasion/metastasis, enabling replicative immortality, and avoiding apoptosis [8].

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Immune response to UVR

While both UVRA and UVRB reach the skin, UVRB can recruit macrophages and neutrophils into the skin [9].

This is because the energy from light induces cell infiltration of melanomas by upregulating Ccr2 [10] and ATF2 [11].

UVRB also induces ligands for the chemokine receptor Ccr2 (only Ccl8, while the expression of other Ccr2 ligands returned to baseline), causing macrophages to produce INF-γ and melanocyte activation, characterized by aberrant growth and migration [10].

An inflammatory positive feedback loop that strengthens macrophage-melanocyte interactions appears.

Surprisingly, IFN-γ (and not type-I interferons) from recruited monocytic cells stimulates melanocyte proliferation, migration, as well as the expression of genes involved in evasion of the immune defense barriers[10].

Anti-IFN-γ antibodies exhibited significantly reduced UVRB-mediated activation of melanocytes [12].

The IFN-γ signaling pathway is involved in the initiation, survival, and/or outgrowth of UVRB-induced melanoma cells, mediating pro-tumorigenic effects [10].

After exposure to UVRB radiation, melanocytes play a role in controlling the skin's immune responses in neonatal mice, with ATF2 being involved in this process.

Additionally, ATF2 mutant animals displayed a reduction in the infiltration of macrophages into their skin [11].

IL-23 inhibits the incidence, growth, and melanoma progression by preventing nevus initiation and growth, reducing metastasis to lymph nodes, and prolonging the survival of transformed melanocytic cells, inhibiting proliferation of melanocytic cell lines, blocking tumor-promoting IFNγ, and inducing melanocyte DNA repair.

Normal melanocytes and nevus cells express IL-12 and IL-23 receptors [13].

Interleukin-6 (IL-6) is a multifunctional immunomodulatory cytokine that is synthesized by a variety of cell types, including melanoma cells.

IL-6 is known to exert a significant influence on the pathophysiology and progression of malignancies.

The suppression of apoptosis and the induction of tumor angiogenesis are mechanisms through which it facilitates the growth of tumors [14].

IL-2, a well-described stimulator of CD8+T cells (CD8 T) and natural killer (NK) cells [15], with minimal modifications in T-regulatory cells, proved useful in metastatic melanoma and renal cell carcinoma.

Despite the low-affinity IL2 receptor beta gamma subunits (IL2Rβγ) and, therefore, the need for high doses, the molecule offered up to 25% durable responses for melanoma treatment [16].

IL-7, IL-15, IL-18 seem to be key supporters of T-cell expansion and function in vivo [17,18].

UVR is well acknowledged as a prominent risk factor in the pathogenesis of cutaneous melanoma.

The accumulation of stochastic mutations in melanocytes, generated by UVR, results in the transformation of these cells and the creation of tumors.

UVR possesses the ability to elicit both localized and systemic immunological responses that are specific to antigens. Consequently, this allows converted melanocytes to evade immune monitoring [19].

Tumors that were highly antigenic and produced by UVR were allografted into syngeneic mice, and these mice were also subjected to UVR. When UVR was not present, the tumors that were inoculated experienced rejection.

Comparable findings in mice with compromised immune systems were reported, indicating that immunological suppression is facilitated by exposure to UVR [20-23] (Figure 1).

Multiple processes have been suggested to be involved in the immune suppression generated by UVR.

These mechanisms encompass impaired antigen presentation, the secretion of immunosuppressive cytokines, and the death of immune cells [24].

Exposure of the skin to UVR has been observed to result in a decrease in the number of Langerhans cells, a specific type of dendritic cell located in the dermis, at the location of exposure [19,22].

Langerhans cells that have been exposed to UVR undergo migration to the lymph nodes, where they exhibit an impaired ability to activate Th1 cells, a crucial component in the initiation of an efficient immune response.

In contrast, the activation of Th2 cells induces immunological suppression through the activation of regulatory T cells [24-26].

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Furthermore, it has been observed that Langerhans cells, which have been exposed to UVR, exhibit impairments in their ability to present antigens in the lymph nodes and experience death when subjected to greater levels of UVR.

This indicates that UVR exposure has the potential to diminish the presentation of tumor antigens to the immune system [19].

During the transformation of immune cells into a state of immunosuppression, there was also observed an elevation in the levels of immunosuppressive cytokines, namely IL-10, IL-4, and TNF-α, which were detected both at the site of action and throughout the entire system[24,26-28].

The exposure to UVR results in a decrease in the cytokine IL-12, causing an alteration in the ratio of Th1 and Th2 cells, with a subsequent increase in the latter population [29,30].

Also, stimulation of Th2 cells by UVR may have a role in the elevated presence of M2-like tumor-associated macrophages (TAMs) observed in individuals with melanoma (Figure 1).

Collectively, these findings indicate that it is advisable to restrict sun exposure when administering immunotherapeutic agents, substances that restore the immune system.

This precaution is necessary because excessive UVR during the treatment protocol could potentially diminish the efficacy of the immunotherapeutic agent."

Impaired Functioning of T-Cells

Cancer cells exploit the immune-checkpoint axis, which involves the interaction between programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1), to their advantage (Figure 1).

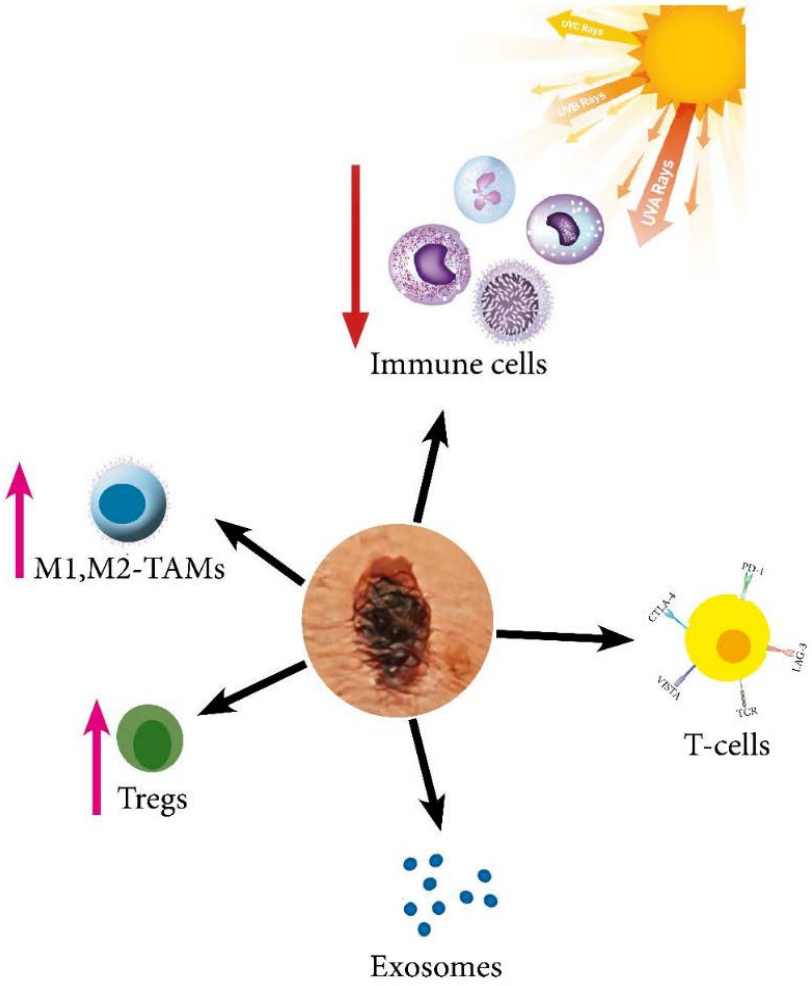

Figure 1. An overview of the immune system dysfunctions that support the onset and spread of melanoma. UV causes systemic and local immune suppression, which lowers immune cell production and function. Cancer cells exploit the immune checkpoint axis through interactions with immune checkpoints expressed on T cells. The cargo carried by exosomes derived from tumors leads to immune suppression, both locally and systemically. Melanoma cells elevate the presence of immune suppressive cells, such as Tregs and MDSCs (M1 and M2-like TAMs)

The PD-1/PD-L1 axis acts as an inhibitor of the immune response and acts as a protective mechanism for the host against autoimmune reactions [31-34]

When a host is infected by a pathogen, T-lymphocytes are recruited and guided to the infection site, where they initiate their immune response against the invading pathogen.

Meanwhile, cells in the nearby healthy tissues deploy a protective mechanism against T-lymphocytes by generating PD-L1.

This molecule facilitates an interaction with the PD-1 receptor found on T-lymphocytes, thereby hindering the subsequent activation of these T-cells.

In the context of cancer, the interaction between PD-1 expressed on cytotoxic T-lymphocytes and PD-L1 found on tumor cells, tumor-associated macrophages, NK cells, dendritic cells, and other immune cells results in the establishment of a state known as T-cell exhaustion.

This condition impairs the immune system's capacity to recognize and eliminate tumors and is induced by epigenetic alterations that occur within T-cells [35-48]**.**

The importance of PD-1/PD-L1 interactions goes beyond the confines of the tumor microenvironment, as they have also been observed in the lymph nodes that drain from the tumor.

These interactions take place between PD-1-expressing T-cells and PD-L1-expressing dendritic cells, contributing to the emergence of an anergic or exhausted T-cell phenotype [49].

The Programmed Cell Death Protein 2 (PD-L2) acts as the alternate ligand for PD-1 and has been detected on both antigen-presenting cells and melanoma cells. PD-L2 shares functional characteristics with PD-L1, functioning as a negative regulator of cytotoxic T-cell activity.

Elevated levels of PD-L1 expression have been noted in melanoma, with specific subtypes of the disease exhibiting varying degrees of this expression.

Cutaneous melanoma displays the highest PD-L1 expression, with a rate of 62%, followed by mucosal melanoma at 44%, acral melanoma at 31%, and uveal melanoma at 10% [39,50-53].

PD-L2 is found in higher abundance compared to PD-L1, and it also exhibits a stronger affinity for PD-1, suggesting that there might be a distinct contribution by PD-L1 and PD-L2 in the modulation of immune responses.

Furthermore, prior research has shown that glycosylation of PD-L1 enhances its stability and strengthens its interaction with PD-1, thereby increasing its ability to induce T-cell exhaustion [54-58].

Cytotoxic T-cells exposed to ongoing tumor antigens become activated and subsequently produce interferon-γ (IFN-γ), then interacts with the IFN-γ receptor found on melanoma cells, initiating the downstream signaling cascade of the JAK/STAT/IRF1 axis.

This cascade activates transcription factors IRF1 and MYC, leading to their binding to the PD-L1 promoter.

Additionally, the involvement of transcription factors STAT3 and IRF1 is essential for the functioning of PD-L2 [59-63].

Various transcription factors, including HIF-1, AP-1, and NF-κβ, have been identified as regulators of PD-L1 expression in melanomas.

However, the specific mechanisms through which they exert their regulatory effects vary due to differences in the mutational landscape [58,64,65].

Upon activation of the T-cell receptor (TCR) through engagement with the antigen/MHC complex, the MAPK and PI3K/AKT pathways are activated, leading to various T-cell activation phenotypes (transcriptional activation, cytokine production, T-cell survival, and proliferation) (Figure 1) [66-70].

In the context of cancer, the interaction between PD-L1/PD-L2 and PD-1 on cytotoxic T-cells has been observed to recruit SHP1/2 to the TCR.

This interaction subsequently affects various phosphorylation activities, resulting in impaired function and metabolism of cytolytic T-cells [36,37,60,69,71-80].

Apart from PD-1, several other immune suppressive checkpoint molecules exist that decrease the activity of cytotoxic T-cells against cancer cells: neuropilin-1 (NRP-1), cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), T-cell immunoglobulin, lymphocyte-activation gene 3 (LAG-3), mucin domain-containing protein 3 (TIM-3), and V-domain Ig suppressor of T-cell activation (VISTA) [81-89].

Multiple trials suggest that administering anti-PD1/anti-PD-L1 treatment for early-stage melanoma may hinder the establishment of durable immune responses.

An alternative strategy to activate suppressed immune cells is the sequential administration of cancer vaccines in addition to anti-PD-1/anti-PD-L1 therapy.

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CTLA-4 is recognized as the second most prominent immune suppressive checkpoint regulator (Figure 1).

The significance of CTLA-4 as a negative regulator of the immune system is evidenced by the occurrence of severe autoimmune disorders in mice lacking CTLA-4, which arises from uncontrolled T-cell activation. CTLA-4 expression on T-cells is responsible for its immunosuppressive effects, achieved by suppressing T-cell activation through competitive binding with CD28 for the ligands CD80/CD86, T process known as "T cell anergy" [82,83,90-94].

The actions of PD-1, PD-L1, and CTLA-4 may have broader implications beyond their established roles as negative regulators of the immune system (Figure 1).

The signaling pathways involving PD-1, PD-L1, and CTLA-4 in melanomas have been shown to potentially impact various aspects of tumor biology (proliferation, growth, metastatic signaling, survival, and the establishment of an immunosuppressive microenvironment around the tumor cells) [95-100].

Exosomes

Both normal and cancer cells release exosomes, but cancer cells release larger quantities compared to normal cells [101].

The cargo carried by tumor-derived exosomes plays a crucial role in activating the pre-metastatic environment and suppressing anti-tumor immune responses, thereby facilitating cancer cell metastasis (Figure 1) [101].

Melanoma-derived exosomes have been observed to migrate to lymph nodes, inducing tumor tolerance and preparing the lymph nodes for the arrival of melanoma cells [102,103].

Exosomes transfer melanoma-derived MHC I towards antigen-presenting cells, decrease the expression of molecules like CD80/CD86, and increase the expression of immunosuppressive cytokines such as IL-6 and TGF-β, resulting in the altered function of antigen-presenting cells and decreased T-cell proliferation [104].

Tumor-derived exosomes interact with T-cells, inhibiting their activation and inducing apoptosis [105-107].

Melanoma exosomes impairs cytolytic function of NK cells and contribute to the formation of myeloid-derived suppressor cells, leading to their accumulation within the tumor microenvironment and suppression of the immune response [107-109].

Melanoma exosomes can activate a mixed population of M1-and M2-like TAMs, with the tumor microenvironment favorizing the M2-like TAM phenotype [110-113].

Also, melanoma cancer cells-derived exosomes have been demonstrated to express the immune control molecule PD-L1 on their membranes, leading to the suppression of the immune response, both locally and generalized [114,115].

Spontaneous Melanoma-Prone Mouse Model

These models accurately replicate the immunological profiles observed in human melanoma patients and display an increase in immunosuppressive myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment, correlating with the presence of anergic gp100-expressing melanoma-specific CD8+T-cells, in the same line with the melanoma patient data.

These models exhibit an inverse relationship between dendritic cell (DC) levels and tumor burden, and restoring DC populations by Flt3L, a growth factor, can enhance cytotoxic cytokine production by T-cells [116-118].

Another study demonstrated an increase in regulatory T-cells (Tregs) (Figure 1), a decrease in CD8+T-cells from the tumor tissues, together with an increase of immunosuppressive cytokines IL-10 and TGF-β, correlating with increasing tumor mass in these mice, and paralleling melanoma patient data.

As tumor burden rises, CD8+T-cell activation markers and lymphocyte proliferative capacity decrease in these models [116].

Defective Immune Recognition of Melanomas by the Immune System

During melanoma progression, there is a process called immune editing, characterized by the selection of subclones based on their ability to evade immune detection, and includes three phases: elimination, equilibrium, and escape [119,120].

In the elimination phase, dendritic cells detect antigenic melanoma clones, capture these melanoma antigens, process them, and present them on their Major Histocompatibility Complex II (MHC II) to naïve T-cells in the lymph nodes, leading to the activation of melanoma-specific cytotoxic CD8+T-cells.

The equilibrium phase involves immune responses eliminating highly antigenic melanoma clones, while some clones escape anti-tumor immune responses.

During the escape phase, low immunogenic melanoma clones proliferate and disseminate rapidly [119].

As melanoma progresses, tumor cells and immune cells that suppress the immune system produce different soluble molecules that interfere with dendritic cells' ability to activate naïve T-cells into effector CD8+T-cells in lymph nodes.

Immunosuppressive cytokines, such as IL-10 can lead to defective antigen presentation by dendritic cells, reducing T-cell activation.

Dendritic cells downregulate membranous expression of MHC II and co-stimulatory molecules CD80/CD86, which are crucial for T-cell activation [121-123].

The expression of CTLA-4, PD-1, PD-L1, and PD-L2 (immune checkpoint molecules), on dendritic cells disrupts their innate immune functions and affects T-cell activation [120,124-129].

Melanoma subclones, during genetic and epigenetic changes, can successfully downregulate essential elements of their MHC I antigen presentation pathways, efficiently evading immune surveillance.

Native melanoma-associated antigens (MART-1/Melan-A, gp100, tyrosinase), are variably expressed in melanoma cells.

As melanoma subclones successfully downregulate MHC I or another melanoma antigen's expression, they can establish an immune-refractory tumor.

Interestingly, melanoma cells express MHC II on their surface, attracting tumor-specific CD4+T-cells that suppress anti-tumoral activity of cytotoxic T-cell by counteracting the IFN-γ pathway of the immune responses [130].

Myeloid-derived suppressor cells (MDSCs) have the ability to undergo differentiation into tumor-associated macrophages (TAMs) and exhibit plasticity by transitioning between M1-and M2-like macrophage phenotypes within the microenvironment of the tumor (Figure 1).

Hypoxic regions present within the tumor have a tendency to induce a shift in TAMs towards an M2-like phenotype, whereas adequately oxygenated conditions promote an M1-like phenotype [3,111,112,131-133].

The progression of melanoma is accompanied by a heightened infiltration of TAMs, with a specific increase in M2-like TAMs.

The ratio of M1 to M2 TAMs has been identified as a significant prognostic indicator [131,134-137].

M1 TAMs have been found to exhibit anti-tumor actions, whereas M2 TAMs have been observed to promote tumor growth. those with melanomas that have a greater abundance of M1 gene signatures seem to have a more favorable prognosis in comparison to those with elevated M2 gene signatures [138,139].

The inhibition of M-CSF receptors on MDSCs has been observed to induce a shift in TAMs towards an M1 phenotype, which is further reinforced by GM-CSF signaling [140].

Furthermore, the inhibition of the macrophage receptor with collagenous structure (MARCO) through the use of an antibody has been shown to facilitate the differentiation of TAMs into an M1 phenotype [141].

The MARCO, which is a scavenger receptor involved in pattern recognition, has been found to be linked to a gene expression profile that resembles the phenotype of M2-like tumor-associated macrophages [141].

The aforementioned findings indicate that the M-CSF and MARCO potentially have a role in regulating the PI3K/AKT/mTOR axis and the polarization of TAMs into M1 or M2 phenotypes [140-146].

Th (Helper T cells) have a crucial function in the regulation of adaptive immune responses.

They accomplish this by stimulating cytotoxic T cells and exerting an influence on the phagocytic and digesting characteristics of macrophages.

The polarization of M1 and M2 macrophages is attributed to two subclasses of Th, namely Th1 and Th2 [138,147].

A Th1 bias has been observed in both healthy individuals and patients who have undergone surgical resection of melanomas.

Nevertheless, it has been observed that in individuals with melanoma, there is a prevalence of Th2 cells, which contributes to the development of chronic inflammation, which further facilitates the evolution of melanoma by causing a shift in the polarization of TAMs towards M2 phenotypes [148-150].

M1 TAMs demonstrate anti-tumor characteristics through the release of proinflammatory cytokines, ROS, nitric oxide, and their ability to function as proficient antigen-presenting cells, hence facilitating adaptive anti-tumor immune responses.

On the other hand, it has been observed that M2 macrophages have a role in promoting the growth of melanoma by facilitating tumor angiogenesis, promoting the function of regulatory T cells to suppress the activity of

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cytolytic T cells, and secreting soluble substances that inhibit immune responses against the tumor [131,151-154].

In the progression of melanoma, there is a notable tendency for M1 TAMs to undergo a phenotypic transition towards an M2.

This shift in phenotype is known to facilitate tumor growth and enable evasion of the immune system.

The enhancement of melanoma treatment results could be achieved by the development of medicines capable of inducing a transition of M2 to M1 TAMs [138,141].

Role of Regulatory T-Cells in Melanoma Immune Evasion

CD4+Tregs have a significant role in the regulation of an exaggerated immune response, thereby mitigating potential harm to the host.

Nevertheless, cancer cells manipulate the identical defensive mechanisms utilized by Tregs in order to evade the immune system. In the context of melanoma, Tregs exhibit an upregulation in their presence within the peripheral blood, lymph nodes, and tumor microenvironment.

This increase in Tregs has been associated with a decrease in the cytolytic activity of immune cells that are responsible for targeting and eliminating tumor cells.

Melanomas employ the strategy of recruiting and stimulating Tregs by the secretion of H-ferratin and chemoattractant cytokines/ chemokines.

This process effectively influences the functionality of Tregs within the localized tumor microenvironment.

Tregs utilize a variety of strategies to inhibit the immune system, which can be categorized into four distinct mechanisms.

These mechanisms involve the secretion of immune suppressive cytokines, namely IL-10, IL-35, and TGF-β, the induction of cytolysis in immune cells, the targeting of dendritic cells, and the disruption of immune cell function through metabolic processes [155-166].

Role of MDSCs in Melanoma Immune Evasion

Myeloid cells play a crucial role in the innate immune system, serving as vital constituents that safeguard the host against pathogens through the processes of phagocytosis and the initiation of inflammatory responses, which in turn recruit other immune cells.

It has been observed that cancer cells have the ability to induce the transformation of myeloid cells located in the bone marrow into MDSCs [167,168].

MDSCs have been identified as key contributors to the advancement of cancer, as they facilitate the spread of tumor cells and impede the functioning of T-cells.

The presence of MDSCs in both the peripheral blood and tumor microenvironment has been observed to be correlated with disease progression, diminished T-cell activity, and prognostic significance in melanoma [117,168-173].

Conclusions

UVR is a well-established risk factor for the development of cutaneous melanoma.

It triggers a cascade of biological effects in the skin, particularly in melanocytes, which can lead to DNA damage and the formation of melanoma lesions.

Melanin and other chromophores in the skin absorb UVR energy, leading to electron excitation.

Prolonged excitation can result in the generation of ROS, chronic inflammation, and immunosuppression, which can alter tissue homeostasis and promote melanoma progression.

Advanced molecular diagnostic methods have identified various genetic mutations, amplifications, and deletions that play a crucial role in melanoma development and survival signaling.

Melanoma cells continually adapt to host defenses, making treatment challenging.

UVR exposure can trigger an immune response, recruiting immune cells like macrophages and neutrophils to the skin.

However, the interplay between UVR and immune responses can lead to melanocyte activation and, in some cases, contribute to pro-tumorigenic effects.

Various cytokines, including IL-23, IL-6, IL-2, IL-7, IL-15, and IL-18, have roles in modulating immune responses in melanoma.

They can either inhibit or promote tumor growth and affect the function of T-cells and other immune cells.

Immune checkpoint molecules like PD-1, PD-L1, and CTLA-4 are exploited by melanoma cells to evade the host immune response.

These molecules lead to T-cell exhaustion, impairing the immune system's ability to recognize and eliminate tumors.

Melanoma-derived exosomes play a significant role in suppressing anti-tumor

immune responses, priming pre-metastatic niches, and facilitating cancer cell metastasis.

They carry various cargo that can inhibit immune cell function.

Melanoma progression involves a process known as immune editing, where tumor cells selectively evade immune detection.

This process includes phases of elimination, equilibrium, and escape, with immune suppression mechanisms playing a crucial role. Myeloid-derived suppressor cells (MDSCs) can transform into tumor-associated macrophages (TAMs) and contribute to an immunosuppressive microenvironment.

M1-like TAMs have anti-tumor properties, while M2-like TAMs promote tumor growth.

Tregs are recruited and stimulated by melanoma cells, leading to immune suppression.

They employ various mechanisms, including the secretion of immunosuppressive cytokines and the targeting of dendritic cells, to inhibit the immune response.

The main findings of this study are summarized in Table 1.

Table 1. Key Findings and Concepts.

Immune Response to UVR	- UVR exposure recruits macrophages and neutrophils to the skin.
	- UVR induces melanocyte activation, IFN-γ production, and immune interactions.
	- Immune responses to UVR can have pro-tumorigenic effects via IFN-γ signaling.
	- ATF2 plays a role in immune responses to UVR radiation.
Cytokines in Melanoma	- Cytokines such as IL-23, IL-6, IL-2, IL-7, IL-15, and IL-18 modulate immune responses in melanoma.
	- IL-2 is used for treating metastatic melanoma.
	- IL-23 inhibits melanoma progression by various mechanisms.
UVR and Immune Suppression	- UVR exposure leads to immune suppression through multiple mechanisms.
	- Langerhans cells are affected by UVR, impairing antigen presentation.
	- Changes in cytokine levels, including IL-10, IL-4, and TNF-α, are observed with UVR exposure.
Impaired Function of T-Cells	- Immune checkpoint molecules such as PD-1, PD-L1, and CTLA-4 play a role in melanoma immune evasion.
	- These molecules lead to T-cell exhaustion and impair immune recognition of tumors.
	- Other checkpoint molecules like TIM-3 and LAG-3 are also involved.
Exosomes	- Tumor-derived exosomes have a significant role in suppressing anti-tumor immune responses.
	- They carry cargo that interferes with immune cell function and promotes tumor tolerance.
	- Melanoma-derived exosomes express PD-L1, further suppressing the immune response.
Spontaneous Melanoma Models	- Spontaneous melanoma-prone mouse models mirror immunological profiles seen in human melanoma patients.
	- These models reveal correlations between MDSCs, Tregs, TAMs, and immune activity.
	- The balance of M1 and M2 TAMs is a prognostic indicator.
Defective Immune Recognition	- Melanoma progression involves immune editing with phases of elimination, equilibrium, and escape.
	- Immunosuppressive mechanisms include reduced antigen presentation and immune checkpoint expression.
	- Melanoma cells can downregulate MHC I and MHC II expression to evade immune detection.
Role of Regulatory T-Cells	- CD4+ Tregs are upregulated in melanoma and contribute to immune suppression.
	- Tregs employ multiple mechanisms, including cytokine secretion, to inhibit the immune response.
	- Their presence correlates with reduced cytolytic activity of immune cells.
Role of MDSCs in Immune Evasion	- MDSCs play a key role in melanoma progression and immunosuppression.
	- They can differentiate into TAMs and contribute to the tumor microenvironment.
	- MDSC levels correlate with disease progression and decreased T-cell activity.

In conclusion, melanoma is a complex and immunologically evasive cancer that exploits various mechanisms to evade the host immune system, including the use of immune checkpoints, the release of exosomes, and the recruitment of immunosuppressive cells.

Understanding these mechanisms is essential for developing effective treatments and immunotherapies for melanoma.

Additionally, minimizing UVR exposure and promoting early diagnosis remain crucial in preventing melanoma development and improving patient outcomes.

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Conflict of interests

None to declare.

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