Book Chapter

Tumor Associated Macrophages (TAMs) Contribution in Melanoma Progression: Potential Molecular Pathways and Proposed Therapies

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Published **January 04, 2023**

How to cite this book chapter: Alaa Skeyni, Hady Al Shami, Hussein Fayyad-Kazan. Tumor Associated Macrophages (TAMs) Contribution in Melanoma Progression: Potential Molecular Pathways and Proposed Therapies. In: Hussein Fayyad Kazan, editor. Immunology and Cancer Biology. Hyderabad, India: Vide Leaf. 2023.

Abstract

The incidence of melanoma continues to escalate worldwide. Its ethology is related to cumulative genetic and environmental factors. However, despite the fact that various genetic mutations were found in metastatic and malignant melanoma, predispositions do not occur equally often. Mutations in BRAF, MAPK, and ERK were observed as landmarks for treatment approaches. Although a global improvement was attained, patients relapsed after a short period and were then diagnosed with a late stage of metastatic melanoma. The need to better understand the tumor microenvironment TME of melanoma became heavily crucial. Out of the cells exhibiting an immunosuppressive phenotype in the tumor microenvironment TME, are tumor-associated macrophages TAMs. The latter result from defects in several pathways, such as JAK/STAT network causing an imbalance between macrophages promoting tumor progression and those suppressing the tumor hence aiding the immune response. Comprehending the link between TAMs and the molecular pathways promoting its aggressive phenotype offers a new avenue to personalized medicine.

Introduction

According to US assessments, skin cancer is the most frequent malignancy among Caucasian populations, with about one in every five Americans contracting some kind of skin cancer [1]. Melanoma is cancer that originates from melanocytes and is the deadliest skin cancer that predominantly affects younger and middle-aged people [2]. It doesn't always emerge on the skin; it can also develop in the eyes, vagina, anus, sinus, and oropharynx, whereas only 5% of melanoma incidence occurs at these sites [2]. Cutaneous melanomas are characterized as either superficial spreading, lentigo malignant, or nodular and acral lentiginous [2]. Malignant melanoma is the most aggressive form of skin cancer, comprising 4% of all skin cancer occurrences but contributing to 80% of vast skin cancer mortality [3]. Globally, it affected 324,600 individuals in 2020, resulting in 57,000 deaths [4].

According to annual cancer status reports issued in the United States in 2020, the incidence of melanoma is steadily growing, regardless of gender [5]. Current therapies, including immune checkpoint treatment, targeted therapy, radiotherapy, and chemotherapy, have resulted in a sustained reduction in the death rates of melanoma (6.1% annually) [5], nonetheless treatments of melanoma still keep room for advancement due to drug resistance [6]. Various studies showed that melanoma has a large tumor mutational burden protecting it from immunity invasion [7,8]. Understanding the precise mechanism of immunosuppression in melanoma has indeed become crucially influential.

The tumor microenvironment (TME) is the complex ecosystem in which tumor cells reside and interact with various types of cells [9]. The former comprises a significant role in tumor progression and drug resistance [10]. Many cells, including fibroblasts, adipocytes, and migratory hematopoietic cells, particularly macrophages, thrive in the tumor microenvironment. Evidence shows that macrophages aid in tumor progression and metastasis. In the tumor microenvironment, macrophages are educated to exhibit a restorative role that induces angiogenesis, matrix breakdown, and tumor-cell motility. TAMs have a focal role in tumor progression and metastasis [9].

A network of signaling molecules, transcription factors, epigenetic mechanisms, and post-transcriptional regulators underly the distinct forms of macrophages' activation. A candidate activator is the canonical JAK-STAT signaling pathway. Upon activation, it drifts macrophages' function toward the M1 phenotype or towards the M2 phenotype according to the transcription activated [10].

While the role of myeloid cells in innate and adaptive immunity has been known for over 100 years, leukocyte detection in tumors goes back to the middle of the nineteenth century. Macrophage's role in tumors was only examined recently, despite the fact that many malignancies are inundated with these cells. Normally, upon tissue damage, cells express various chemokines and growth factors to recruit circulating monocytes

to the site of impairment. Macrophages serve as an immune system mediator to kill pathogens and aid tissue repair. TAMs, on the other hand, are lured by tumor cells, and a specific stimulus repurposes their innate immune activity to guard against tumor progression. As the presence of TAMs in human cancers is concomitant with poor prognosis in more than 80% of studies, we further explore the role of TAMs in melanoma and their distinct stimulating molecular networks [11]. Here, we describe skin melanoma disease and focus on mechanisms that induce the immunosuppressive phenotype of TAMs and their effect on tumor progression and dissemination depending on emerging data.

Skin Melanoma

Biology of Melanoma

Melanoma is the deadliest form of skin cancer. Melanocytes are neural crest-derived cells and can be found mainly in the basal epidermis and hair follicles, in addition to mucosal surfaces, meninges, and the choroidal layer of the eye [12]. Skin keratinocytes produce melanocyte-stimulating hormone (MSH), as a response to UV-induced DNA damage, which binds to the melanocortin receptor 1 (MC1R) on melanocytes, prompting them to generate and release melanin. The melanin pigment ultimately operates as a shield from UV radiation, thus preventing further DNA alteration [13]. However, melanin has a complex of anti-oxidant and pro-oxidant properties [14], and the conversion of melanin from an antioxidant to a pro-oxidant agent under the influence of various etiological factors such as UV radiation, heavy metals, and herbicides, marks a critical pathogenetic event that initiates carcinogenesis. Melanin's pro-oxidant action causes a rise in the quantities of intracellular oxygen radicals, which results in damage to the melanocyte's DNA molecule. These mutations would result in excessive activation of various cell signaling pathways leading to uncontrolled proliferation and cancer [15].

Risk Factors

The risk factors for the development of melanoma are related to both the human body and the environment.

Exposure to ultraviolet radiation is the leading risk factor for the development of melanoma where both natural sunlight and artificial lighting systems are ultraviolet radiation sources [16]. The UVB wavelength between 290 and 320 nm is by far the most carcinogenic to the skin [17]. Those UVB waves are mostly absorbed by the nuclear proteins and acids of melanocytes leading to oxidative stress, which disrupts the latter [18]. Recent studies concluded that intermittent exposure to sunlight is one of the major risk determinants for melanoma [19].

Environmental factors contribute to a variation in melanoma incidence globally. The etiology arises from the fact that people residing at lower latitude are at higher risk of melanoma, where Australia and New Zealand record the highest incidence [20]. Scandinavia and Northern Europe record the highest incidence in Europe whereas the lowest incidence of melanoma there is in Eastern and Southern Europe [21]. Socioeconomic status and occupation impact melanoma development in individuals, coming from the fact that sun exposure acts as a major risk factor. Individuals receiving immunosuppressive treatments, and patients diagnosed with immunodeficiency syndrome are more susceptible to melanoma progression [22].

Genetic factors highly contribute to melanoma occurrence, as a family history of melanoma accounts for high-risk probability of malignancy. Mutations in various genes are the main driving force in melanoma as they initiate cell proliferation and cessation of apoptosis as a normal response to DNA damage [23].

Autosomal dominant alleles were present in the familial inheritance of melanoma and exceeded the first generation [19]. NRAS is one example of genes that are particularly altered in 15–20% of melanoma cases [24]. Another mutation is the BRAF gene, which occurs in about 50% of melanoma cases. BRAF kinase plays a role in the regulation of the signaling pathway

between mitogen-activated protein kinase and extracellular signal-regulated kinase (MAP/ERK), which controls cell division and differentiation. As a result, this mutation causes uncontrollable division of melanocytes, which culminates in the onset of melanoma [25]. Individuals with predispositions are demonstrated to develop melanoma at a younger age (40 years old) [22], and in such situations, medical surveillance at a young age might assist better prognosis.

Diagnosis

Physical examination requires general skin inspection. Moles described as the ugly ducklings exhibit a phenotype distinctive from other moles and are further inspected following a criteria covering the asymmetry, border, color, diameter, and evolution (ABCDEs) [26].

A biopsy from the suspected skin lesion is fundamental for melanoma diagnosis confirmation. It's typically performed with local anesthesia using 1 of 3 techniques: saucerization shave biopsy, punch biopsy, or narrow excision with 2-mm margins. The sample should assess the invasion depth (Breslow thickness) covering the surrounding healthy tissue as well [27].

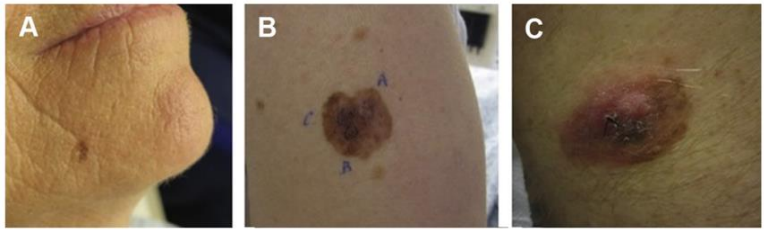

Figure 1: Clinical illustartion of melanoma where (A) Melanoma in situ on sun damaged skin can exhibit few features except for irregularity of pigmentation and early dermato-scopy signs. (B) T1 melanomas can develop a prominent radial growth phase, initially growing outward, but careful examination demonstrates gray stippling in the area marked "C" as evidence of early invasion. (C) Late-stage tumors, such as this T3 lesion, have developed a vertical growth phase and developed a nodule in this preexisting nevus. Vertical growth phase and nodular components of melanomas can grow rapidly and are more likely to be amelanotic [26].

Treatment

The majority of newly diagnosed melanoma patients have an early-stage illness, for which surgical excision is the therapy of choice. Such therapy is curative in the vast majority of instances. [28]. However, some patients will later relapse with metastasis dissemination, while approximately 10% of melanoma cases are diagnosed at an advanced stage and are unresectable or already metastatic. Approximately one-third of stage IV cancers had visceral and brain involvement at diagnosis, which is consistent with a poor prognosis and a reduced likelihood of a sustained response to treatment [29].

In the second line of defense comes drug therapy. In cases of metastatic melanoma, the most efficient choice would be chemotherapy. Until recently, dacarbazine remains to be the traditional chemotherapy used with a survival rate of only 27% in one year. The invention of novel medications with high efficacy and minimal toxicity is one of the limitations of chemotherapeutic development.

Several targeted therapies are selected to deal with melanoma mutations. The most promising targeted drugs are BRAF inhibitors, which permit excellent efficacy in patients with BRAF mutations. Yet, 50% of patients relapse due to secondary resistance only shortly after receiving the treatment. Several underlying mechanisms, including tumor suppressor gene PTEN loss, cyclin D amplification, MEK mutations, NF1 loss, and others, drive tumor cells to become resilient to BRAF inhibitors.

The fact that many sufferers still are diagnosed at a late stage of the illness necessitates the development of innovative treatments for advanced melanoma. Melanoma cells can bypass and avoid the immune response attributed to their profoundly mutagenic nature. Tumor cells in melanoma can diminish MHC1 expression, reducing antigen recognition by TCR on T cells. In addition, immune inhibitory substances such as suppressive cytokines, TGF-, and PGE2 are emitted [11].

Another trick melanoma cells use to evade the immune response, is to express programmed cell protein PD1 that inhibits the activity of T cells hence promoting self-tolerance [11].

Three Prominent types of immune-based treatments exist: cancer vaccines, adoptive cell therapies, and immunomodulatory strategies.

Cancer vaccines are administered to patients in the late stages of melanoma. It includes sensitization of the immune system against tumor antigens. The tumor's capacity to evade the immune response is the strategy's only drawback. In light of this, no melanoma vaccination is authorized for clinical use [30].

Immune therapies including the administration of interleukin-2 to promote tumor T-cells proliferation, elicited limited response in patients with high toxicity.

Nowadays, immunotherapies showing curative effects are immune checkpoint inhibitors. Nivolumab and ipilimumab are antibodies against PD-1 and CTLA4 respectively, that can block the checkpoint-manipulating virulence that melanoma exhibits. Treatment with antibodies blocks the binding to respective ligands and consecutive signals that promote immune tolerance. Treatment with these drugs has already shown durable survival for up to 10 years in 20% of patients with stage IV melanoma. Though these tactics demonstrate remarkable progress, they have pitfalls such as encouraging self-tolerance, which frequently causes inflammation in the gastrointestinal tract, skin, and endocrine organs [31].

Despite the breakthrough, immunotherapeutic drugs have been recorded in melanoma treatment, a considerable number of patients still don’t benefit efficiently or develop secondary resistance. Conducting further research would help understand why patients acquire resistance after benefiting from a certain treatment, are there specific biomarkers that aid in choosing the most efficient treatment and reducing the severe side effects? There is no magic potion for treating melanoma, hence prioritizing personalized treatment. Such a treatment is initiated

with thorough research on tumor environment residents and molecular networks involved.

Molecular defects in Melanoma

Somatic mutations in melanoma don't occur at the same frequency, but often rearise in signaling pathways responsible for cell proliferation, growth and metabolic, cell cycle control, cell identity, replicative life span, as well as those controlling resistance to apoptosis [32].

Staring BRAF mutations in cancers lead to further interest in the subsequent molecular pathways. Mitogen-activated protein kinase (MAPK) signal transduction pathway gained focus lately because of the major role BRAF plays in its activation. Additionally, NRAS, MEK1/2, and ERK. Mutations in the G protein subunit alpha 11 (GNA 11) are activating, leading to the production of an overactive Gα11 protein that stimulates uncontrolled proliferation of the pigment-producing cells (melanocytes) in the uvea or the skin. As in cancerous tumors, the G protein subunit alpha q (GNAQ) gene mutations in uveal melanoma result in an overactive protein, which leads to excessive signaling. This abnormal signaling likely contributes to the overgrowth of cells and tumor formation [33].

As previously mentioned, despite using inhibitors of aberrant proteins implicated in cell cycle control, numerous melanoma patients still exhibit resistance against therapy. One of the ubiquitous features of such cases is the presence of cells promoting tumor growth and suppressing the immune response such as tumor-associated macrophages.

Macrophages and Tumor Microenvironment

TAMs (Tumor-Associated Macrophages) are critical to the development, maintenance, and eradication of cancer cells. In general, macrophages in the tumor microenvironment can be polarized into two functional states M1 and M2 macrophages. Classically activated macrophages, or M1 polarized macrophages, are those that emit pro-inflammatory and immune-

stimulatory cytokines like interleukin 12 and 23, after being aroused by cytokines like interferon-gamma. M1 macrophages can have anti-tumoral properties, by scavenging and destroying phagocytosed tumor cells and stimulating helper cell type 1 responses. M2 polarized macrophages, also known as alternatively activated macrophages, are activated by Interleukin 4, 10 and 13. Most TAMs are thought to resemble M2 macrophages. These cells play an important role in connecting inflammation with cancer. Expressing high levels of anti-inflammatory cytokines, scavenging receptors, angiogenic factors, and proteases compared to M1 type counterparts. TAMs can reprogram the immunosuppressive microenvironment and promote the proliferation, invasion, and metastasis of tumor cells. They can stimulate tumor angiogenesis, and inhibit anti-tumor immune responses mediated by T cells [34].

As TAMs are mostly similar to M2 macrophages in their phenotypic traits, studies have demonstrated that the presence of TAMs is associated with poor survival in various tumor types [35,36]. Nevertheless, the TME is observed to contain a variety of macrophage subtypes, reflecting its intricacy [37]. TAMs participate in tumor progression by interacting with both tumor and other stromal cells where these tumor cells reverse the function of macrophages making them an adjunct to the tumor. This allows TAMs to promote tumor proliferation, angiogenesis, immune evasion, invasion, and metastasis [38].

TAMs in Melanoma

Tumors are known to contain varying numbers of macrophages. In melanoma, the macrophage content ranges from 0 to 30% of the total cells of the tumor. Metastasizing melanomas, as well as metastatic lesions, all contain <10% of macrophages, whereas non-metastasizing tumors have widely varying numbers of macrophages [39]. The two categories of TAMs, M1 and M2, have opposing tumor-promoting and tumor-suppressing roles, this leads TAMs to playing a dual role on tumor proliferation, invasion and metastasis, angiogenesis, and resistance to treatment.

Regulating Tumor Proliferation, Invasion and Metastasis

Studies showed that the increased number of M2 macrophages promotes melanoma growth [40], whereas the M1 polarization of macrophages inhibits the proliferation of melanoma [41]. Several reasons might lead to the polarization of one type of macrophage over the other. One example is macrophages deficient in integrin β3 inducing the polarization of the M2 macrophage phenotype [42]. The survival analysis of melanoma patients treated with isolated hepatic perfusion showed that M1 polarization was associated with higher overall survival of patients, due to M1 macrophage inhibitory effects on melanoma proliferation [43].

The increased expression of Connexin 43 which is a vital gap junction protein in the TME has been reported to induce M1 polarization, which in return inhibited the invasion and migration of melanoma cells in vitro [44]. On the other hand, M2 macrophages that lack tripartite motif 59 (TRIM59), which belongs to the TRIM family of proteins, promote the expression of Matrix metallopeptidase 9 (MMP-9) and mucosal vascular addressing cell adhesion molecule 1 (MAdCAM-1). Being mentioned, they are implicated in tumor migration and invasion [45].

The ability of TAMs to communicate with other immune cells in the TME is intriguing [46]. For example, the nuclear factor of activated T cells (NFAT1) is a transcription factor that can bind to IL-2 and regulate its expression promoting T cell activation. It has also been proved to increase the infiltration of M2 macrophages, thus promoting TAM-mediated growth and metastasis in melanoma [47].

Angiogenesis Alteration in Melanoma

A vital process in the preparation of lymph nodes for melanoma metastasis would be angiogenesis [48]. Studies showed that M1 TAMs trigger immune responses and normalize irregular tumor vascular networks, which sensitize cancer cells to chemotherapy and radiotherapy thus suppressing tumor growth [49]. On the

other hand, increased M2 polarization of TAMs stimulates tumor angiogenesis, leading to tumor progression in return [50]. This is attributed to the induction of endothelial cells by melanoma exosomes promoting the expression of Granulocyte-macrophage colony-stimulating factor (GM-CSF). This enhances the activity of hypoxia-inducible factor-2α (HIF-2α) in M2-like TAMs, which attenuates vascular endothelial growth factor (VEGF) activity by inducing the production of soluble VEGFR-1, promoting improved tissue and vasculature patency [48].

Resistance to Melanoma Treatment

Recent studies indicate that macrophages serve a role in melanoma resistance, where the different phenotypes of macrophages either promote resistance in melanoma or improve the efficacy of drugs in the treatment of melanoma [51]. An approach that achieved durable responses hand in hand with immunotherapy, is targeting immune checkpoint molecules such as programmed cell death protein 1 (PD-1) [52], but 25% of patients with melanoma who have shown an objective response to PD-1 blockers also develop resistance [53]. This resistance is due to increased frequencies of M2-polarization TAMs, which link to the high levels of IL-34 induced by PD-1 inhibitors [54]. In addition, blocking the binding of G protein-coupled receptor 4 (GPCR4) on TAMs to its ligand R-spondin 1-4 can reduce the polarization of M2 macrophages on one hand, and promote the polarization of M1 macrophages, on the other hand, further enhancing the efficacy of PD-1 immunotherapy in melanoma treatment [55].

JAK-STAT Pathway and TAMs

A wide range of processes required for homeostasis and development in mammals are mediated by the Signal transducer and activator of transcription (STAT) signaling [56]. It is shown that STAT activation induces a myriad of cytokines and growth factors that drive events as varied as hematopoiesis, immune fitness, inflammation, tissue repair, adipogenesis, and apoptosis [57]. It should come as no surprise that any STAT signaling flaws that cause either global deregulation or overactivation cause the

disease to manifest and worsen [58]. . Additionally, the STAT family, to a large extent, regulates the distinction between immune responses that inhibit and those that promote cancer [59].

The extracellular binding of numerous cytokines and other ligands with their corresponding transmembrane receptors results in the activation of receptor-bound Janus kinases (JAKs). The latter eventually stimulates the phosphorylation and subsequent homo- or heterodimerization of resting STAT monomers in the cytoplasm.

This Cascade of events accounts for STAT activation. Activated STAT dimers would translocate to the nucleus and bind to specific target genes inducing their activation and further modulation of downstream targets [60]. The JAK family involves four kinases JAK1, JAK2, JAK3, and TYK2 [61], whereas the STAT protein family consists of seven members: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 [61]. Several STAT members including STAT3 and STAT5 are linked to tumor initiation and progression while others (STAT1 and STAT2) are integral in antitumor defense and in maintaining an effective and long-term immune response [56]. The STAT family proved to have a central role in the polarization of myeloid cell functions as well as in tumor progression and the alteration of immune response to cancer. STAT1, STAT3, and STAT6 orchestrate a massive role in transmitting polarizing signals to the nucleus and have distinct roles in macrophage polarization [62].

Available data suggest that STAT1 acts as a tumor suppressor and negative regulator of tumors. Its activity is essential for the antiproliferative effects of interferons. In most patients with resistant human melanoma, the loss of STAT1 activity was detected [63]. The STAT1 transcription factor is essential for mediating melanoma cell sensitivity to various pro-apoptotic stimuli. One example is the ability of STAT1 to regulate the expression of death-receptor-4 (DR4) expression on melanoma cells, which could affect (TNF-related apoptosis-inducing ligand) TRAIL sensitivity [63]. The major event required for

recruiting M1- macrophages is the participation of NF-KB and STAT1 along with interferon regulatory factor IRF9, P53. Disruption in this corporation leads to M1phenotype conversion towards the immunosuppressive phenotype of TAMs [10]. Evidence indicates that STAT1 activation is essential for immune surveillance against tumors [64]. One study showed that mice deficient in either the IFN-γ receptor (signaling that activates STAT1) or STAT1 displayed enhanced resistance to the induction of tumors by methylcholanthrene [65].

As it promotes distinct transcriptional patterns in response to a range of growth factors, cytokines, hormones, and oncogenes (e.g., IL6, leptin, IL12, IFNs, IL10, GCSF, prolactin, growth hormone, EGF, HGF, bFGF, v-Src, v-Fps, and v-Sis), the STAT3 transcription factor is critical in this context [63]. In malignant cells where STAT3 activation is constitutive, this protein is a key mediator in promoting cell proliferation, angiogenesis, and apoptosis inhibition. It also activates the transcription of genes important for invasion and metastasis [63]. This malignant profile of STAT3 is exhibited by its ability to activate various genes responsible for tumor progressions such as c-myc and cyclin D1. As well as one that inhibits apoptosis (Bcl-xL, survivin), and promotes metastasis (matrix metalloproteinases) [63]. It is shown that STAT3 is constitutively activated in diverse tumor-infiltrating immune cells, including TAMs and its activation is associated with M2 macrophage polarization [10]. STAT3 directly induces the expression of the M2 marker CD163, both in macrophages and tumor cells [66]. Additionally, IL6 inhibition of M-CSF-induced colony formation observed in animals is abolished in mice mutated for the gp130-STAT1/3 signaling, suggesting that the IL6/STAT3 pathway could regulate macrophage homeostasis [67].

TAM-Targeting Therapies in Melanoma

Given the vital role of macrophages in melanoma progression and several other tumors, targeting macrophages is considered a promising potential therapeutic strategy. This would give rise to two primary approaches to melanoma treatment: Conventional therapies, including surgery, chemotherapy, radiotherapy and

targeted therapy with reduced side effects on one hand, and reducing or reprogramming TAMs on the other [68]. The current TAM-related approaches for melanoma treatment include:

Reducing the Number of TAMs in Melanoma: Deleting or Recruitment Inhibition

Direct deletion of TAMs poses an attractive alternative to improve the prognosis of a patient with melanoma. One example is the colony-stimulating factor 1 receptor (CSF1R) which can control the differentiation, proliferation, and survival of macrophages [69]. It is present in the vast majority of macrophages and targeting it seems to be an effective method for depleting TAMs in tumors. Clinical trials have shown that targeting CSF1R or combining it with other therapies, can result in improved treatment outcomes for patients [68].

Another approach would be reducing the number of TAMs in the TME by inhibiting their recruitment. One way would be inhibiting CCL2 which is involved in recruiting monocytes and giving rise to TAM expansion. This method was able to delay tumor progression in several experimental tumor models, including melanoma. Since there is a lack of evidence on thisstrategy, more research is recommended [70].

Activating Macrophages in Melanoma

It is proven that some TAMs have antitumor effects and suppress tumor growth by activating immune responses while other TAMs promote tumors [71]. This suggests that TAMs are flexible, and reprogramming them to treat tumors would be a reasonable therapeutic approach. It was demonstrated that melanoma cells can block macrophage activation by suppressing toll-like receptor (TLR) signaling [72], hence, a clinical study tested the efficiency and safety of TLR7 ligands (852A) in the treatment of melanoma and found that combining an agonist of TLR (3M-052 for TLR7/8), which polarizes macrophages towards a pro-inflammatory phenotype, with a checkpoint blockade is more efficient than a checkpoint blockade alone in the treatment of B16-F10 melanomas [73].

Adoptive Macrophage Therapy

Adoptive cellular therapy and chimeric antigen receptor (CAR) T cells have achieved marked success in the treatment of lymphoma and leukemia, among others [74], which allows the possibility of using adoptive transfer of engineered active macrophages as a treatment for melanoma. The technique uses the artificial administration of special drugs, cytokines, and even gene editing to promote macrophages that are cytotoxic to tumor cells [75]. Chen et al [76] have reported that CAR-macrophages could be utilized as a novel immunotherapy candidate against solid tumors. However, this technique is far from any clinical application as the mechanism of action of adoptive macrophage therapy is not fully understood.

Furthermore, the current successful trials of the monoclonal antibodies (mAb) acting as checkpoints inhibitors are coming to the surface. A recent study shows that the expression of (macrophage receptor with collagenous structure) MACRO which is a pattern recognition receptor of the class A scavenger receptor family, was shown to be overexpressed in TME in cancers with poor prognosis [34]. Expression of MACRO was identified in TAMs in murine melanoma TME. The former is promoted by the tumor and M2-polarizing cytokines [77]. Secondly, MACRO expression correlates to M2 TAM and EMT-metastasis driving gene profile in human metastatic melanoma. Providentially, immunotherapy targeting MACRO arrested tumor growth and metastasis and increased TME immunogenicity [77]. Overall, employing mAb to rewire TAMs is a viable method of treating melanoma.

Conclusion

In summary, melanoma is the deadliest form of skin cancer, showing a high risk of metastasis and resistance to available therapies. Seeking new prognostic markers to recognize patients at high risk of developing metastases became imperative. Exhibiting a tumor-promoting phenotype, TAMs appear to be a target for novel therapies. Clarifying the link between malignant tumors and TAMs proposes novel biomarkers for prognosis,

diagnosis, and therapy. Meanwhile, clear differentiation between M1 and M2 polarized macrophages is essential. The two types of macrophages exist as two extremes upon a continuum, with the balance being tipped one way or the other by higher or lower levels of cytokines in the tumor environment. Macrophages are plastic, therefore M1 macrophages give the respective stimuli in the right environment and can become more M2-like, and vice versa. Dissecting networks like JAK-STAT, MAPK, and the role of PD-1 expression could open a new window toward safe and subtle therapeutics against melanoma. Mechanistically, enhancing TME's immunogenicity by antibodies that target Tams specifically will liberate T cells to fight the cancer onslaught, which may also be helped by anti-CTLA4 therapy. These therapies elucidated the role performed by the immune system in the cancer battle.

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