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Mechanisms of Myeloid-Derived Suppressor Cells-Mediated Immunosuppression in Melanoma

Lei Tang[1,a,*]

[1]*College of Food Science and Technology, Guangdong Ocean University, Gudangdong, 524094, China*
a. 11231124yy@stu.gdou.edu.cn
**corresponding author*

Abstract: Melanoma is a malignant tumor with immunosuppression. Its immunosuppression is mostly due to myeloid-derived suppressor cells (MDSCs). At present, many studies have found that the generation of tumors is accompanied by the upregulation of certain factors and call them tumor markers. Some markers that cause tumor immunosuppression have been found in melanin. However, it is not clear how these markers work at the molecular level. The production of MDSCs, their migration into the tumor microenvironment (TME), their impact on T cells, and their unique function in the signal regulation pathway are all examined in this article. This study provides some references on pathways such as TLR4/NF-κB, STAT3/Arg1 mRNA, such as STAT3/CCR5mRNA, etc. For the future research on the immunosuppression of melanoma. The pathways discovered so far are only a small part, and there are more pathways to be discovered. Future research can focus on the discovery of new pathways.

Keywords: Melanoma, immunosuppression, myeloid-derived suppressor cells, TLR4.

1. Introduction

One of the primary causes of melanoma patients' poor survival rates is immunosuppression. In the process of immunotherapy, due to the immunosuppression of melanoma, the treatment of melanoma is hindered by many obstacles [1], Therefore, current research needs to find a way to relieve its immunosuppression. Numerous investigations have demonstrated that one of the main causes of melanoma immunosuppression is MDSC's inhibition of T cells. This study focuses on MDSC to study how it is generated, recruited, and causes damage to T cells. MDSC is produced by immature myeloid cells regulated by factors in the TME, and is affected by multiple pathways, recruited to the TME, and suppresses T cells in the TME [2]. According to this study, the pathway that affects MDSCs the most is toll-like receptor 4 (TLR4)-NF-κB. It is affected by regulatory factors and affects downstream pathways, leading to T cell inhibition. The primary mechanism of T cell inhibition is the production of PD-L1 by MDSCs, which lowers cell energy and causes the TME to consume a lot of L-arginine and L-tryptophan, resulting in famine [3,4]. C-C chemokine receptor type 5 (CCR5) is the primary factor influencing MDSC recruitment in the TME [5]. Based on the above-known information, this study continues to explore the specific mechanisms of activation and regulation of various pathways. Tumor-derived extracellular vesicles contain heat shock protein 90α (HSP90α), which can lower T cell energy and raise PD-L1 expression on bone marrow cells [6]. The primary source of the calcium-

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binding protein S100A9 is immune cells like neutrophils and monocytes. It suppresses T cell activity, lowers T cell energy, and increases PD-L1 expression on MDSCs, just like HSP90α [7]. The pleiotropic cytokine interleukin-6 (IL-6) is involved in a number of cellular processes as well as inflammatory reactions.T cell starvation and activity inhibition result from its upregulation of MDSC arginase (Arg) 1 expression [8]. MicroRNAs contribute to the immunosuppression of melanoma in addition to controlling and expressing proteins. The expression of PD-L1 is upregulated by melanoma EV-associated microRNA (miR) [9]. Among them, HSP90α, S100A9, and microRNAs all act on immature myeloid cells (IMCs) by activating TLR4/NF-κB. One important component of MDSC's capacity to have immunosuppressive effects is not just its production but also its recruitment inside the TME. Prior research has demonstrated that the interaction between chemokines and chemokine receptors, particularly CCR5, mediates the recruitment of MDSC.

Research has shown that CCR5 expression on MDSC can be upregulated by IL-6, GM-CSF, and IFN-γ. Additionally, it creates a dependence on the signal transducer and activator of transcription (STAT).

2. Generation of myeloid-derived suppressor cells (MDSCs): related pathways

MDSCs are produced by a variety of signaling pathways that induce immature myeloid cells (IMCs) to exhibit traits that influence T cells, such as elevated PD-L1 expression and upregulated Arg1 expression. According to this study, the LTR4/NF-κB pathway is connected to the majority of the signaling pathways that influence the production of MDSCs. Numerous upstream factors interact with TLR4 to activate NF-κB, which in turn increases the expression of specific genes in MDSCs, including Arg1 and PD-L1, demonstrating their capacity to suppress immunity. Furthermore, the immunosuppressive function of MDSCs may also be impacted by signaling pathways linked to STAT3. In studies related to the effects of IL-6 on MDSCs, it was found that IL-6 can increase the production of PD-L1 in MDSCs, which is carried out through the STAT3 pathway [8]. Previous studies have found that the recruitment of MDSCs in the TME is mainly affected by CCR5: the interaction between chemokines accumulated in the TME and CCR5 attracts MDSCs to the tumor [5]. The upregulation of CCR5 expression is also STAT3-dependent. MDSCs affect T cells in a variety of ways, such as increasing the consumption of L-arginine and L-tryptophan to starve T cells and upregulating PD-L1 to inhibit T cells.

2.1. HSP90α

Previous studies have shown that TEVs can transform normal myeloid cells into MDSCs [10]. TEV contains HSP 90α, which is necessary for myeloid cell transition. A study showed that human recombinant HSP90α (rHSP90α) alone upregulates PD-L1 on monocytes by isolating CD14 monocytes from the peripheral blood of healthy donors. The study discovered that the increase of PD-L1 expression may be prevented by inhibiting anti-TLR4 mAb and TLR4 inhibitors. However, this inhibition was not mediated by blocking anti-TLR2 mAb or isotype control mAb, suggesting that rHSP90α indeed bind to TLR4.Furthermore, following 16 hours of treatment with rHSP90α, human monocytes showed increased expression of Indoleamine 2,3-dioxygenase 1 (IDO-1) protein levels, and the elevation of PD-L1 was eliminated by the addition of the NF-κB inhibitor Bay. Further studies found that this was mediated by NF-κB and TLR4-dependent mechanisms. The results demonstrated that neither blocker had extra blocking effects when co-cultured with anti-PD-L1 antibodies and the IDO-1 inhibitor 1-D-MT in comparison to anti-PD-L1 or anti-IDO-1 monotherapy. This suggests that HSP90α interacts to TLR4 to activate NF-κB and upregulate IDO-1 in MDSCs during the process by which TEV transforms normal myeloid cells into MDSCs.IDO-1 causes PD-L1 of monocytes to

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upregulate this pathway. Therefore, HSP90α activates NF-κB after binding to TLR4, and the activated NF-κB upregulates IDO-1 and causes PD-L1 to upregulate, causing T cell inhibition [6].

2.2. miRs

In addition to HSP90α in TEV, which can transform iMC into MDSC, TEV-related microRNA can also make iMC show immunosuppressive activity. A family of highly conserved non-coding RNAs known as miR plays a crucial role in post-transcriptional regulation of gene expression [11].A study has used lipid transfection of synthetic miR-125a-5p to imitate miR trafficking in EVs [9].Through an NF-κB-dependent mechanism, the transfer of this miR-125a-5p mimic caused these cells to exhibit immunosuppressive behavior. Using the RET tg melanoma model, this study examined the relationship between miR-125a-5p levels and melanoma progression. The findings imply that miR-125a-5p plays a crucial component in controlling MDSC activity within the TME. In myeloid cells, several miRs have been found to bind to endosomal TLRs.The upregulation of PD-L1 expression in miR125a-5p-treated iMCs was significantly reduced when NF-κB activation was blocked with BAY-11-7082 or BOT-64, which prevented phosphorylation of NF-κB inhibitor β. This suggests that miR/TLR4/NF-κB is the pathway that causes the upregulation of PD-L1 expression in iMCs in the regulation of MDSCs.MiR-125a-5p mimic transfection not only induced PD-L1, but it also increased the production of ROS and IL-6, two variables linked to MDSC activity. Consequently, miR-125a-5p binds to TLR4, triggers NF-κB, and increases PD-L1, IL-6, and ROS expression. T cells are inhibited when these factors are overexpressed [9].

2.3. S100A9

Calprotectin A and B (S100A8 and S100A9) levels have been reported to be elevated incancer and show a positive correlation with tumor progression and metastasis [12,13]. As a TLR4 ligand, S100A9 can activate MDSC in malignancies [14]. Studies have shown that monocytes were treated with S100A9 for 72 hours. By blocking T cell proliferation tests with or without TLR4 inhibitors, the immunosuppressive potential of treated monocytes was assessed. The significant elevation of PD-L1 expression and ROS generation was inhibited by the TLR4 inhibitor resatorvid. Monocytes treated with S100A9 showed enhanced expression of IDO-1, although restored decreased this expression, suggesting that TLR4 signaling plays a role in IDO upregulation. The phosphorylation expression of MAPK, NF-κB, and STAT3 rose under the action of S100A9, while restored decreased their phosphorylation expression. This suggests that TLR4 influences numerous downstream pathways following binding to S100A9 and activation, which results in the production of MDSC. Increased TLR4 and RAGE protein expression was seen with S100A9, suggesting that TLR4 signaling-mediated NF-κB activation results in TLR4 expression upregulation. Therefore, S100A9 binds to TLR4 to activate MAPK, NF-κB, and STAT3, and NF-κB causes IDO-1 to upregulate [7].

2.4. HMGB1

The receptor for advanced glycation end products (RAGE) is liganded by HMGB1 [14]. Moreover, HMGB1 binding raised the phosphorylation expression of MAPK, NF-κB, and STAT3. TLR4 inhibitors (but not RAGE inhibitors) reduced the expression of MAPK phosphorylation and STAT3 phosphorylation in monocytes. Both inhibitors decreased p-NF-κB expression intensity [7].In monocytes, HMGB1 produced less immunosuppressive action and MDSC-related marker expression than S100A9. An MDSC-like phenotype was acquired by monocytes treated with HMGB1, primarily via the TLR4 signaling pathway, indicating that RAGE's function is less significant in this situation. This implies that TLR4 is more favored by HMGB1 than RAGE [7].Therefore, HMGB1 and TLR4

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can also phosphorylate MAPK, STAT3 and NF-κB; binding with RAGE can phosphorylate NF-κB, and the phosphorylation of NF-κB can also induce the inhibition of T cell activity [7].

2.5. IL-6 and GM-CSF

To identify the variables and molecular processes that control immunosuppressive indicators at the mRNA and protein levels, a study employed the immortalized myeloid suppressor cell line MSC-2, primary immature myeloid cells, and in vitro differentiated MDSC. The function of CD8 T cells was significantly suppressed by MDSCs that developed in the presence of IL-6 [8]. The expression of Arg1 mRNA, which is crucial for MDSC-mediated immunosuppression, can be strongly stimulated by IL-6, and Arg1 activity is likewise elevated. The research team was able to remove the notable IL-6-induced elevation of Arg1 mRNA expression after employing the STAT3 inhibitor Stattic, suggesting that Arg1 overexpression is STAT3-dependent. PD-L1 expression can be significantly increased by GM-CSF alone, but IL-6 does not further raise PD-L1 expression, and GM-CSF cannot induce MDSC to create ROS on its own. MDSC differentiated with IL-6 and GM-CSF exhibited considerably higher Arg activity compared to cells differentiated with GM-CSF alone, which is consistent with the discovery that IL-6 can upregulate Arg1 mRNA. ROS generation was also greatly increased in these cells. Thus, through STAT3, IL-6 increases Arg1 activity, Arg1 mRNA expression, and ROS; PD-L1 and ROS can be upregulated by GM-CSF [8].

3. Recruitment of MDSCs

Chemokines and chemokine receptors (CCRs) [15], specifically the interaction between CCR5 [5], drive the recruitment of MDSCs to malignancies.IL-1β, TLR ligands lipopolysaccharide Pam3CSK4 and R848 and CCR5 ligands CCL3, CCL4, and CCL5 were unable to increase Ccr5 expression at the mRNA level. On the other hand, Ccr5 expression was considerably raised by IL-6, GM-CSF, and IFN-γ [8].In one study, MSC-2 cells were stimulated with CCR5 ligands and the chemokines CCL3, CCL4, and CCL5. It was discovered that these chemokines did not increase the expression of corresponding genes, such as Pdl1, Tgfb, Arg1, Nos2, Ido, and Cox2. Additionally, IMC stimulated with CCR5 ligands for 24 hours was unable to stop the proliferation of activated T cells. This demonstrates that MDSC-mediated immunosuppression is not exacerbated by CCR5.The STAT3 inhibitor Stattic reversed the overexpression of CCR5, and the elevation of surface CCR5 was dependent on STAT3. As a result, inflammatory stimuli such IL-6, GM-CSF, and IFN-γ encourage the recruitment of MDSC in the TME by upregulating the expression of CCR5 on MDSC via STAT3 [8].

4. Pathways by which MDSCs affect T Cells

There are several ways that MDSCs can impact T cells. T cell starvation is primarily responsible for some of them. Because Arg1 and inducible nitric oxide synthase (NOS2) are highly expressed in the TME, MDSCs are able to ingest L-arginine [16]. Moreover, T cell starvation is induced by reducing L-tryptophan through increased indoleamine-2,3-dioxygenase (IDO) expression [17]. Furthermore, MDSCs produce reactive oxygen species (ROS) and nitric oxide (NO) as a result of NOS2 and nicotinamide adenine dinucleotide phosphate oxidase (NOX), which harm anti-tumor T cells [18,19]. Others, like PD-L1, which decreases T cell inhibition, directly block T cell pathways by upregulating binding sites.

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5. Conclusion

This article mainly points out several signaling pathways that have a greater impact on MDSC in melanoma. HSP90α, S100A9, HMGB1 and microRNAs affect TLR4/NF-κB, IL-6/STAT3/Arg1mRNA, IL-6/STAT3/CCR5mRNA. MicroRNAs, HMGB1, HSP90α, and S100A9 all interact with TLR4 to raise monocyte PD-L1 levels. These variables impact other variables and raise the PD-L1 level. Additionally, HMGB1 and S100A9 stimulate the generation of ROS and the release of inflammatory mediators; HSP90α raises IDO-1 levels6; microRNAs encourage the synthesis of IL-6. After monocytes were treated with S100A9 or HMGB1, TLR4 not only increased PD-L1 but also the phosphorylation of MAPK p38, NF-κB p65, and STAT3.The IL-6/STAT3 pathway had an impact on CCR5 in the investigation of the melanoma MDSC recruitment route. The study found that CCR5 only affected the migration and recruitment of MDSC and did not inhibit the activity of T cells. GM-CSF and IFN-γ could also increase the mRNA expression of CCR5. Through STAT3, IL-6 can also increase MDSC's Arg1 mRNA expression and activity. Furthermore, there was a notable increase in ROS generation in MDSC differentiated with GM-CSF and IL-6. Depletion of L-arginine and L-tryptophan inhibits T cells in the melanoma TME; MDSC nitric oxide (NO) and reactive oxygen species (ROS) harm anti-tumor T cells due to NOS2 and nicotinamide adenosine dinucleotide phosphate oxidase (NOX); overexpression of PD-L1 can also inhibit T cells by causing insufficient energy in T cells. The TME is a complex signaling network, with interactions between different factors and pathways, making melanoma difficult to treat. In the future, the main approach to treating melanoma will be to discover more pathways and cells that regulate tumors in the microenvironment and create more effective targeted drugs.

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