Development and Status of Therapeutic Strategies Targeting MDSCs in Lung Cancer Immunotherapy

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Abstract. Myeloid suppressor cells (MDSCs) exert immunosuppressive effects in the lung cancer microenvironment through various mechanisms, including metabolic regulation, cell surface molecular action, and secretion of immunosuppressive cytokines, which weaken the host's anti-tumor immune response and promote tumor growth and immune escape. This study focused on the role of key signaling pathways (such as JAK/STAT, PI3K/Akt/mTOR, NF-κB) and its related genes (ARG1, iNOS, PD-L1, S100A8/A9) in immunosuppression during the development and differentiation of MDSCs. In addition, the paper summarizes current therapeutic strategies targeting MDSCs, including ARG1 and iNOS inhibitors, PD-L1/PD-1 immune checkpoint inhibitors, and innovative therapies blocking the S100A8/A9 pathway, and explores the potential of multi-target combination therapy. However, the heterogeneity of MDSCs, poor treatment selectivity, side effects and treatment resistance remain major challenges. Further studies should concentrate on the design of multi-target combination therapy strategies, the targeting selectivity optimization, and reliable biomarkers to continue further increasing efficacy and safety in immunotherapy for lung cancer.

Keywords: Lung cancer, MDSCs, ARG1, iNOS, PD-L1, scRNA-seq, Tumor microenvironment.

1. Introduction

In lung cancer, which is a major global killer when it comes to cancer, and even with progress in precision medicine and immunotherapy, long-term survival is very low. An important reason for this is the ever-changing tumor microenvironment (TME), which has cancer cells, immune cells, and other supporting cells along with various extracellular matrix components. Apart from providing all the necessary conditions for the sustenance and metastasis of cancer, the TME also aids in promoting the mechanism through which the cancer cells can escape being detected by the immune system.

The major factors that regulate immune responses within the TME are myeloid-derived suppressor cells (MDSCs). They are a heterogeneous population of immature myeloid cells which are induced to proliferate under pathological conditions, primarily cancer [1]. These cells suppress the proliferation of T cells, impede the action of natural killer (NK) cells, and secrete immunosuppressive cytokines, thus providing all necessary prerequisites for tumor development. There is a real need to study in detail the mechanisms of immune suppression mediated by MDSC because these cells, acting as the indicators of unfavorable prognosis, establish a critical role in the creation of the resistance to therapies like immune checkpoint inhibitors (ICIs).

This article zooms in on three critical aspects of MDSC biology and their starring role in lung cancer:

1. The signaling pathways that regulate MDSC development and differentiation:

MDSCs expand and acquire function as the signaling pathways directed by tumor-derived cytokines, the pathways involve such as JAK/STAT, PI3K/Akt/mTOR, and NF-κB, and respond as well to other cytokines observed in tumor development orchestrate the differentiation of myeloid progenitors into immunosuppressive MDSCs. This review of the pathways will be important in the identification of possible therapeutic targets.

2. The key immunosuppressive mechanisms of MDSCs:

At the center of the functionality of MDSCs are molecules such as arginase-1 (ARG1), inducible nitric oxide synthase (iNOS), and programmed death-ligand 1 (PD-L1). These contribute to the evasion of the immune response by depleting essential nutrients, increasing oxidative stress, and

expressing molecules that stop T-cell function. Understanding these will provide insight into how MDSCs can suppress antitumor immunity.

3. Therapeutic strategies that can be used to target the immunosuppressive activity of MDSCs in lung cancer:

Approaches include ARG1 inhibitors to restore L-arginine concentration, iNOS inhibitors to diminish NO levels and, thus, oxidative stress, and inhibitors of signaling pathways leading to PD-L1 expression to oppose immune checkpoint suppression. Combination therapies involving agents targeting MDSC immunosuppressive pathways articulated above and conventional immunotherapies are also being pursued as means to circumvent resistance and improve clinical outcomes [2].

The definitions of key terms, their relevance to lung cancer immunotherapy, and a structural preview of the article will be attempts to underscore the above facts, if achieved. This fact will be an importance of MDSCs in tumor progression and therapeutic resistance. The information to be obtained from this study will thus help in efforts to develop new treatment strategies that can better the outcome of lung cancer patients.

2. Investigate the Main Signaling Routes and Molecular Mechanisms in the Growth and Maturation of MDSCs

Signals in the tumor microenvironment regulate the development and differentiation of myeloid suppressor cells (MDSCs). Such major plasticity signals control expansion and differentiation, specificity, and strength of the immunosuppressive function of MDSCs. In lung cancer, signaling pathways are abnormally activated to enhance the immunosuppressive potency of MDSCs through several different layers. This eventually contributes toward immune escape by the tumor. The following sections will concentrate in greater detail on the differential versus common features of key signaling pathways downstream of effectors on MDSCs regulatory function and impact on the immune system.

2.1. Core Role of Key Signaling Pathways

2.1.1. JAK/STAT Signaling Pathway

The JAK/STAT signaling pathway is at the center of the regulatory mechanism for MDSC development, particularly how STAT3 is activated [3]. In the lung cancer microenvironment, GM-CSF, G-CSF and IL-6 secreted by tumor cells and other cells promote the proliferation of MDSCs and enhance their immunosuppressive function by activating STAT3. STAT3 upregulates genes associated with cell proliferation and inhibitory function, such as Bcl-XL (anti-apoptosis gene), ARG1 (arginase 1), and iNOS (nitric oxide synthase). In addition, STAT3 further enhances the accumulation and function of MDSCs by preventing the differentiation of myeloid precursor cells into mature immune cells.

2.1.2. NF-κB Signaling Pathway

The NF-κB signaling pathway also plays an important role in the expansion and immunosuppressive function of MDSCs. The activation of NF-κB depends on inflammatory factors such as TNF-α and IL-1β, which activate NF-κB through the IKK complex and induce the expression of key cytokines such as IL-6 and GM-CSF, thereby indirectly enhancing the activity of the JAK/STAT pathway [4]. In addition, NF-κB directly up-regulated the expression of immunosuppressive molecules such as PD-L1 and TGF-β, further enhancing the inhibitory ability of MDSCs on effector T cells.

2.1.3. PI3K/Akt/mTOR Signaling Pathway

The PI3K/Akt/mTOR pathway plays an important role in the metabolic regulation and differentiation of MDSCs. Growth factors and chemokines in the tumor microenvironment promote mTOR activity by activating PI3K and Akt, which not only meet the needs of MDSCs in a high metabolic state, but also up-regulate the expression of immunosuppressive molecules such as PD-L1

and IL-10. Unlike JAK/STAT and NF-κB, the PI3K/Akt/mTOR pathway is more concerned with MDSCs metabolic reprogramming, especially the regulation of lipid and glucose metabolism, thereby enhancing the survival and function of MDSCs in the tumor microenvironment.

2.1.4. Notch Signaling Pathway

Notch signaling maintains immaturity and enhances immunosuppressive function by regulating the differentiation of MDSCs into specific subtypes, such as G-MDSCs and M-MDSCs. Studies have shown that Notch signaling has a synergistic effect with NF-κB, co-upregulating the expression of IL-10 and TGF-β, while preventing the transformation of MDSCs into mature antigen-presenting cells.

2.2. Differences and Synergies of Signal Pathways

Although the above signaling pathways play a significant role in regulating the development and function of MDSCs, their downstream functions are distinct:

1. Common ground: JAK/STAT, NF-κB, PI3K/Akt/mTOR and Notch pathways all directly enhance the immunosuppressive ability of MDSCs by up-regulating the expression of immunosuppressive molecules (such as ARG1, iNOS, PD-L1, IL-10 and TGF-β). In addition, these pathways promote the accumulation of MDSCs in the tumor microenvironment by blocking the normal differentiation of myeloid precursor cells.
2. Differences: JAK/STAT directly promotes the proliferation and survival of MDSCs through STAT3-mediated gene transcription. NF-κB is more concerned with the regulation of inflammatory factors and amplifies the immunosuppressive signal in TME. PI3K/Akt/mTOR emphasizes metabolic reprogramming to support the high energy requirements of MDSCs; Notch, on the other hand, ensures diversity and functional specificity of MDSCs through subtype differentiation and state maintenance.
3. Synergistic effect: These signaling pathways do not exist in isolation, but co-shape the function of MDSCs through cross-regulation. For example, NF-κB up-regulation of IL-6 and GM-CSF activates JAK/STAT signaling, while metabolic regulation of the PI3K/Akt/mTOR pathway also provides energy support for downstream functions of other signaling pathways. This synergistic effect further amplifies the immunosuppressive effect of MDSCs.

2.3. Brief Summary

MDSCs development and orientation are based on signaling pathways cross-regulating among which JAK/STAT, NF-κB, PI3K/Akt/mTOR and Notch pathways are major. Downstream, these pathways have functions that overlap and are distinct and significantly up-regulate the immunosuppressive ability of MDSCs through synergy [5]. A comprehensive grasp of the pathways and mechanisms of interaction would supply novel concepts for the targeted suppression of MDSCs and equivalent fresh directions in immunotherapy for lung cancer.

3. The Contribution of MDSCs to Immunosuppression in Lung Cancer

In lung cancer, MDSCs suppress anti-tumor immune responses mainly through their metabolic control over cell-surface molecular mechanisms and immunosuppressive cytokine secretion. The last, or collaborative mechanisms more generally, may compromise effector T cell and NK cell functions in the promotion of tumor growth and spreading. Additionally, synergies among different mechanisms make the tumor more immunosuppressive. We will begin with the major mechanism, detail its specific roles, and compare how similar and different they are.

3.1. Metabolic Regulation

MDSCs regulate immune cell function at a metabolic level, primarily in the pathway of consumption of different amino acids and the generation of several active molecules.

Amino acid consumption is one of the important ways that MDSCs exert immunosuppressive effect. MDSCs highly express arginase 1 (ARG1), which breaks down arginine in the tumor microenvironment. Arginine is an essential nutrient for T cell proliferation and activation, and its deficiency blocks T cell proliferation and reduces its function. In addition, arginine depletion inhibits T cell receptor (TCR) signaling, further reducing effector T cell activity. MDSCs also restrict T cells' access to cysteine by absorbing it from the microenvironment, thereby inhibiting T cells' glutathione synthesis and weakening their antioxidant capacity and function.

MDSCs further disrupt immune cell function by producing active molecules. MDSCs produce large amounts of nitric oxide (NO) through inducible nitric oxide synthase (iNOS), and release reactive oxygen species (ROS) and active nitrogen (RNS) molecules [6]. These molecules not only disrupt the mitochondrial function of T cells, but also induce apoptosis. At the same time, ROS and RNS can also interact with MHC molecules of antigen presenting cells, reducing antigen recognition ability and further weakening immune response.

Although amino acid consumption and the production of active molecules have different mechanisms of action, their ultimate goal is to weaken T cell function. Arginine depletion achieves immunosuppression by blocking nutrient supply, while ROS and RNS disrupt T cell function by directly interfering with cell structure and signaling. The synergistic effect between the two is particularly evident, with arginine deficiency promoting overproduction of ROS and RNS, further enhancing the immunosuppressive effect.

3.2. Cell Surface Molecular Action

MDSCs interact directly with effector T cells through high expression of immune checkpoint molecules, thereby inhibiting their function. The main immune checkpoint molecules include PD-L1 and CTLA-4.

PD-L1 is one of the most important immune checkpoint molecules on MDSCs. By binding to PD-1 on the surface of T cells, it blocks T cell receptor signaling and inhibits T cell activation and proliferation. Activation of the PD-L1/PD-1 axis also down-regulates the activity of the glycolytic pathway in T cells, further weakening the effector function of T cells, thereby exacerbating the immune escape phenomenon.

CTLA-4 is another key suppressor of MDSCs. It blocks T-cell co-stimulatory signaling by competitively binding B7 (CD80 and CD86). This mechanism not only affects the activation of initial T cells, but also weakens the proliferation and survival of effector T cells, further suppressing the immune response.

Although PD-L1 and CTLA-4 inhibit T cell function through different mechanisms, their common goal is to achieve immune escape. PD-L1 works primarily by affecting downstream signaling pathways in T cells, while CTLA-4 works by blocking initial co-stimulatory signaling. The synergistic effect of the two ensures the comprehensiveness of the immunosuppressive effect, from the activation of T cells to the function of the inhibition.

3.3. Immunosuppressive Cytokine Secretion

Immunosuppressive cytokines secreted by MDSCs, such as TGF-β and IL-10, play a key role in maintaining the immunosuppressive nature of the tumor microenvironment.

TGF-β not only directly inhibits the function of effector T cells and NK cells, but also promotes the expansion of regulatory T cells (Tregs). Tregs further enhance the immunosuppressive function of MDSCs by releasing inhibitory factors, forming a vicious cycle and further aggravating immune escape.

IL-10 reduces the recognition of tumor antigens by T cells by inhibiting the maturation and antigen presenting ability of antigen presenting cells (APCs). At the same time, IL-10 can also induce polarization of M2-type macrophages, further enhance the immune escape ability of tumor microenvironment, and help tumor cells escape immune surveillance [7].

Although both TGF-β and IL-10 can exert immunosuppressive effects by inhibiting effector T cells and indirectly enhancing the function of MDSCs, they differ in specificity. The role of TGF-β in the expansion of Tregs is more prominent, while IL-10 mainly affects the function of APCs and macrophages. They work together to promote immunosuppression of the tumor microenvironment.

3.4. Differences and Synergies between Mechanisms

MDSCs construct a complex immunosuppressive network through three major mechanisms: metabolic regulation, cell surface molecular action and immunosuppressive cytokine secretion. The core goal of these mechanisms is to weaken T cell function and promote tumor immune escape. Metabolic regulation is mainly through destroying nutrient supply and triggering oxidative stress, while cell surface molecules directly inhibit T cell function by blocking signaling pathways, and the secretion of immunosuppressive cytokines further changes the immune balance of the entire microenvironment. Metabolic depletion provides the basis for the function of immunosuppressive molecules, and at the same time, the expression of PD-L1 works synergistically with the secretion of TGF-β/IL-10, further enhancing the inhibitory effect on T cells. The crosstalk of the different mechanisms played a major role in upregulating the immunosuppressive capacity of MDSCs, hence facilitating tumor immune escape.

3.5. Concise Summary

Metabolic regulation, cell surface molecular action and immunosuppressive cytokine secretion play their specific roles in MDSCs in lung cancer immunosuppression, and, through somewhat as yet ill-defined means of synergy, in building a highly inhibitory tumor microenvironment. Such knowledge of the precise and concerted mechanisms would underpin the rational design of therapeutic strategies aimed at MDSCs.

4. The Contribution of Genes and Proteins Related to Lung Cancer Immunosuppression in Modulation of MDSCs

The MDSCs (myeloid suppressor cells) will exert their suppressive effects in the lung cancer microenvironment through the regulation of gene and protein expression. These genes and proteins will influence the development and differentiation of MDSCs and will also be involved in the direct regulation of their downstream functions, an action that should then itself affect the activation and proliferation of T cells, immunosuppressive cytokine secretion in them, and the action of immune cells. This section will explore the various critical genes and proteins that are directly related to MDSCs in lung cancer immunosuppression and attempt to delineate their cross talks and positive interactions in the tumor immune escape process.

4.1. ARG1 and Immunosuppression

ARG1 is a highly expressed enzyme in MDSCs and it primarily exerts its immunoregulatory function by catalyzing l-arginine degradation. l-arginine is an essential amino acid necessary for T cell proliferation and clonal expansion. The enhanced expression of ARG1 results in the depletion of this amino acid, thereby suppressing the activation and proliferation of T lymphocytes. Inadequacy of l-arginine also suppresses the function of T cells by affecting the T cell receptor signaling pathway along with the mTOR pathway. In addition, the effects of ARG1 are not limited to T cells, but also promote the secretion of immunosuppressive cytokines (such as IL-10 and TGF-β) from MDSCs, enhancing the support of tumor immune escape. These cytokines further enhance the tumor immunosuppressive microenvironment by inhibiting the function of effector T cells and natural killer cells (NK cells) and promoting the expansion of regulatory T cells (Tregs).

4.2. iNOS (inducible nitric oxide synthase) and Immunosuppression

iNOS (inducible nitric oxide synthase) is another enzyme that is highly expressed in MDSCs and primarily inhibits T cell activity by producing large amounts of nitric oxide (NO). NO can not only damage the mitochondrial function and DNA of T cells, leading to T cell apoptosis, but also reduce the recognition ability of T cells to tumor antigens by modifying MHC molecules on the surface of antigen-presenting cells through nitrification. NO produced by iNOS further inhibits T cell activation and proliferation by inhibiting T cell receptor signaling, especially by interfering with key kinases (such as ZAP-70 and LCK) through nitrification. At the same time, iNOS activation also promotes the secretion of immunosuppressive cytokines (such as IL-10 and IL-6) by MDSCs and other immune cells, intensifying the immunosuppressive effect. Unlike ARG1, iNOS enhances tumor immune escape by directly interfering with T cell signaling and cell function [8].

4.3. PD-L1 (programmed death ligand 1) and Immunosuppressive Effects

PD-L1 (programmed death ligand 1) is an important immune checkpoint molecule on the surface of MDSCs, which inhibits the activation and function of T cells by binding to PD-1 on the surface of T cells. The binding of PD-L1 and PD-1 can not only block the transmission of T cell receptor (TCR) signal, inhibit T cell proliferation and cytokine secretion, but also induce T cell apoptosis. In addition, the expression of PD-L1 down-regulates the expression of multiple proliferative and anti-apoptotic genes in T cells, further weakening their anti-tumor ability. By interacting with PD-1 on the surface of T cells, PD-L1 effectively blocks T cell activation by inhibiting T cell co-stimulatory signals such as CD28 and IL-2, limiting the occurrence of immune responses. PD-L1 can also promote the secretion of immunosuppressive cytokines such as IL-10 and TGF-β by MDSCs, further weakening the function of T cells and NK cells. Compared with the effects of ARG1 and iNOS, PD-L1 achieves immunosuppression mainly by inhibiting T cell signaling and enhancing immune checkpoint pathway.

4.4. S100A8/A9 (calc-binding protein A8/A9) and Immunosuppressive Effects

S100A8 and S100A9 are highly expressed calc-binding proteins in MDSCs, and the heterodimers formed play an important role in the aggregation and immunosuppressive function of MDSCs. By interacting with its receptors (such as TLR4 and RAGE), S100A8/A9 promotes the survival and expansion of MDSCs, and activates downstream signaling pathways (such as NF-κB and MAPK pathways) to up-regulate the production of ROS and NO, further enhancing the immunosuppressant function of MDSCs. In addition, S100A8/A9 expression is also associated with tumor cell adhesion and metastasis. By enhancing ROS production, S100A8/A9 inhibits T cell activity, leads to DNA and mitochondrial damage of T cells, induces apoptosis, and reduces the expression of co-stimulatory molecules on the T cell surface. S100A8/A9 can also promote the secretion of immunosuppressive cytokines such as IL-10 and TGF-β by MDSCs, further enhancing the immune escape effect.

4.5. Brief Summary

The role of genes and proteins associated with MDSCs in lung cancer immunosuppression is realized through the synergistic action of multiple molecular mechanisms. ARG1, iNOS, PD-L1 and S100A8/A9 genes and proteins play an important role in regulating immune cell function, affecting T cell activation and secreting immunosuppressive cytokines. They improve the immune getaway ability of the tumor environment through varied paths, which helps tumor cells avoid immune checkups. Knowing the exact ways these genes and proteins work will give a good base formaking immunotherapy plans that target MDSCs, to make the treatment of lung cancer better.

5. Current Therapeutic Strategies Targeting Genes and Proteins Associated with MDSCs

In the last few years, scientists have developed various therapeutic approaches to target gene and protein suppressive roles of myeloid suppressor cells (MDSCs) against immunosuppression in lung

cancer. Therapeutic approaches which have been used to suppress or block the immunosuppressive activity of MDSCs and restore and enhance the host's anti-tumor immune response The major therapeutic strategies are developed to target major molecules, which play an essential role in MDSCs, such as: ARG1, iNOS, PD-L1, and S100A8/A9. By now, these targeted therapies have their own characteristics and have been gradually entering into the stage of clinical research.

5.1. Therapy That Targets ARG1 and iNOS

Two major immunosuppressive factors in MDSCs are ARG1 and iNOS. ARG1 can do a direct job in hindering activation plus proliferation of T cells by consuming arginine. Just to support information: INOS interferes with the function of T cells and can provide apoptosis by the production of nitric oxide. There are various molecules of inhibitor known so far which do target these two. For instance, the iNOS inhibitor L-NMMA and 1400W, along with INCB001158/CB-1158 which are inhibitors for ARG1. All have already shown their efficacy in some preclinical studies plus some early clinical trials. These drugs are designed to restore effector T cell function by restoring arginine levels in the tumor microenvironment or reducing NO production.

However, the separate application of ARG1 and iNOS inhibitors may face therapeutic limitations, as they mainly target one mechanism of MDSCs. In the complex environment of tumor immune escape, a single target may not be sufficient to completely reverse the immunosuppressive effects of MDSCs. Therefore, these treatment strategies are often used in combination with other immunotherapies, such as PD-1/PD-L1 immune checkpoint inhibitors, to improve efficacy.

5.2. Therapy Targeting PD-L1

The PD-L1/PD-1 immune checkpoint pathway is another key immune escape mechanism in MDSCs. The binding of PD-L1 to PD-1 on the surface of T cells inhibited the activation, proliferation and cytokine secretion of T cells. PD-L1 targeted immune checkpoint inhibitors, such as Pembrolizumab and opdivo, have achieved significant clinical effects in a variety of cancers such as non-small cell lung cancer, and have become an important means of current treatment for lung cancer [9].

Although PD-L1 inhibitors have a good effect on some patients, some patients respond poorly to this treatment, the main reason may be the further suppression of the immune system by MDSCs. To overcome this limitation, researchers are exploring the use of PD-L1 inhibitors in combination with other therapies targeting MDSCs, such as ARG1 or iNOS inhibitors. Combination therapy may break the immunosuppressive effect of MDSCs and enhance the anti-tumor immune response through multi-target intervention.

5.3. Therapy Targeting S100A8/A9

S100A8 and S100A9 are highly expressed calc-binding proteins in MDSCs, which promote the aggregation and immunosuppressive function of MDSCs by binding to receptors such as TLR4 and RAGE. Studies have shown that blocking the interaction of S100A8/A9 with its receptor helps reduce the accumulation of MDSCs and restore the function of effector T cells.

Although this treatment strategy has shown promising promise in animal models, the current research is still in the early stages and clinical application is not yet sufficient. Therefore, S100A8/A9 targeted therapy, which is currently mainly used as an adjunct regimen, may be more effective when combined with other therapies such as immune checkpoint inhibitors.

5.4. Combination Therapy

Therapeutic strategies targeting MDSCs are often used in combination with other anti-tumor immunotherapies in the hope of enhancing the therapeutic effect. For example, the combination of ARG1 and iNOS inhibitors with PD-1/PD-L1 immune checkpoint inhibitors has shown more significant efficacy. This multi-target combination therapy enhanced the patient's response to immunotherapy by restoring T cell function and reducing the immunosuppressive effect of MDSCs.

In addition, combinations of chemotherapeutic agents and MDSCs targeted therapies (such as 5-FU in combination with PD-1 inhibitors) have also shown potential to enhance anti-tumor effects. By combining treatment strategies with different mechanisms, the role of MDSCs in tumor immune escape can be broken to a greater extent and the overall efficacy can be improved.

5.5. Brief Summary

At present, therapeutic strategies targeting MDSCs have made some progress in lung cancer immunotherapy. Different targeted therapies have their advantages and disadvantages, and single application may have limitations, so multi-target combined therapy is an effective way to improve the efficacy. Future studies will shed more light on the safety and efficacy of these treatment strategies, while exploring how to maximize patient immune response and survival through individualized treatment regimens.

6. Deficiencies and Challenges

Although targeted therapeutic strategies targeting genes and proteins associated with MDSCs (myeloid suppressor cells) have shown some promise and progress in lung cancer immunotherapy, these therapies still face multiple deficiencies and challenges in practical application. Here are the main issues:

6.1. Heterogeneity and Complexity of MDSCs

MDSCs are a highly heterogeneous cell population consisting of two major subtypes: granulocyte-like MDSCs (G-MDSCs) and monocyte-like MDSCs (M-MDSCs), each with distinct characteristics, functions, and immunosuppressive mechanisms in different tumor microenvironments. This heterogeneity makes single-targeted treatment strategies often limited in effectiveness, as therapies targeting one subtype may not effectively inhibit the function of another subtype. For example, certain ARG1 or iNOS inhibitors may have a good effect on the activity of G-MDSCs but a limited effect on M-MDSCs and vice versa. In addition, the number and functional status of MDSCs vary significantly between patients, further increasing the complexity of treatment. Therefore, there is a need to develop multi-target combination therapy strategies that can simultaneously target multiple subtypes and multiple functional pathways to more fully inhibit the immunosuppressive effects of MDSCs.

6.2. Treatment Options and Side Effects

Current therapeutic strategies for MDSCs, especially inhibitors that target ARG1 and iNOS, suffer from poor selectivity. These inhibitors not only act on tumor-associated MDSCs in vivo, but may also affect ARG1 or iNOS expression in other normal immune cells and tissues, causing adverse reactions. For example, ARG1 and iNOS have normal physiological functions in multiple organs and tissues, such as being involved in the regulation of amino acid metabolism and oxidative stress response in the liver, kidneys and lungs. Therefore, non-selective inhibition can lead to systemic toxicity, such as cardiovascular problems, liver function impairment, and the risk of infection associated with immunosuppression. In addition, PD-L1 inhibitors may cause serious immune-related adverse events (such as colitis, thyroiditis, and dermal toxicity) in some patients, which also limits their use in certain populations. How to improve the targeting and selectivity of these treatments, while reducing side effects, is an important question for future research to address.

6.3. Treatment Resistance and Tumor Immune Escape

Although immune checkpoint inhibitors targeting PD-L1/PD-1 have achieved significant efficacy in some patients, a significant number of patients do not respond to these treatments or develop secondary resistance after the initial treatment is effective. This treatment resistance is often closely related to the persistence of MDSCs and their immunosuppressive function. MDSCs not only inhibit T cells through direct pathways (such as the expression of PD-L1), but also evade recognition by the

immune system through a variety of indirect mechanisms. For example, MDSCs can secrete immunosuppressive cytokines such as IL-10 and TGF-β, inhibit the function of effector T cells and natural killer cells, and promote the expansion of regulatory T cells (Tregs) and M2 macrophages, further consolidating the immunosuppressive environment. In addition, MDSCs may also express novel immune checkpoint molecules (such as LAG-3, TIM-3, and VISTA) that are unaffected by existing PD-1/PD-L1 inhibitors, thus continuing to help tumor cells evade immune surveillance. Therefore, the solution to the problem of therapeutic resistance requires the development of new targeting strategies to address these multiple immune escape mechanisms [10].

6.4. Lack of Biomarkers

The current lack of valid and reliable biomarkers to predict patient response to MDSCs targeted therapy poses a significant challenge to the development of personalized treatment strategies. The number, activity, subtype composition, and pattern of interaction with other immune cells such as Tregs and DCs of MDSCs vary significantly from patient to patient, so a single biomarker is often insufficient to predict therapeutic effect. In addition, the dynamic changes in the tumor microenvironment and the evolution of MDSCs within it increase the complexity and difficulty of monitoring. The lack of appropriate biomarkers makes it difficult to accurately assess the effectiveness of targeted MDSCs therapy and also limits early detection and adjustment of treatment resistance. Therefore, there is an urgent need to develop new combinations of biomarkers that combine the characteristics of multiple immune cells and their functional states to better guide individualized therapy.

6.5. Complexity of Clinical Transformation

Although therapeutic strategies targeting MDSCs have had some success in laboratory and animal models, translating these approaches into clinical applications faces multiple challenges. MDSCs in animal models and MDSCs in human patients differ significantly in gene expression profiles, functional properties, and behavior in the tumor microenvironment, making it difficult to replicate animal results clinically. In addition, many MDSCs targeted therapy strategies are still in early clinical trials, and more large-scale studies are needed to verify their efficacy, safety, and optimal use. In addition, in clinical trial design, issues such as patient heterogeneity, complexity of treatment combination strategies, and differences in responses between different patients need to be overcome. These issues complicate the development and rollout of new treatments.

6.6. Brief Summary

Although therapeutic strategies targeting MDSCs show potential in the field of lung cancer immunotherapy, their practical application still faces many shortcomings and challenges. Future studies should pay more attention to the heterogeneity of MDSCs and their complex immune regulatory networks, develop multi-target combination treatment protocols, improve treatment selectivity and safety, overcome treatment resistance, and search for effective biomarkers to guide individualized treatment strategies. These efforts are expected to promote the clinical application of MDSCs targeted therapy and improve the therapeutic outcomes and prognosis of lung cancer patients.

7. Outlook and Future Directions

Future studies that will clarify the mechanisms by which MDSCs exert their suppressive functions in lung cancer and their interactions with other immunosuppressive cells will be important for the further development of combination treatment strategies. In addition, basic studies on gene and protein targets related to MDSCs need to be enhanced, particularly regarding new drug and treatment regimens for the heterogeneity and treatment selectivity of MDSCs. Developable, traceable biomarkers for predicting and monitoring patient response should also be one of the future research

directions. It would improve, to some extent, the efficacy of treatments related to MDSCs and facilitate more viable immunotherapeutic options for patients.

8. Conclusion

Myeloid suppressor cells (MDSCs) play an important immunosuppressive role in the tumor microenvironment of lung cancer by regulating multiple genes and proteins, such as ARG1, iNOS, PD-L1, and S100A8/A9. They weaken the host's anti-tumor immune response through a variety of pathways, including metabolic regulation, cell surface molecular interactions, and secretion of immunosuppressive cytokines, so that tumors can effectively evade the surveillance of the immune system. Therefore, targeted therapy strategies for MDSCs and their related genes and proteins have become a research hotspot in recent years, and have shown certain clinical potential.

Currently, therapies targeting MDSCs mainly include ARG1 and iNOS inhibitors, PD-L1/PD-1 immune checkpoint inhibitors, strategies to block the S100A8/A9 pathway, and combination therapy with multiple targets. These treatments can weaken the immunosuppressive function of MDSCs to a certain extent, and restore and enhance the anti-tumor ability of T cells and other immune cells. However, the efficacy of a single targeted strategy is limited and often needs to be combined with other treatment modalities to achieve a more significant clinical effect.

Though the therapies against MDSCs have achieved a limited success, they are laden with many inadequacies and challenges. To start with, due to the high heterogeneity and complexity of MDSCs, single-targeted therapy has often proved suboptimal, and thus, a multitarget combination therapy is required. Next, urgent attempts should be made to address the issues of poor selectivity in treatment and potential side effects in order to prevent unspecific damage to normal immune cells and tissues. Another aspect is that most of the patients do not respond as some may develop tolerance toward the existing options of treatment, here an imperative need is felt to design novel targeting strategies to combat the multiple immune escape pathways orchestrated by MDSCs. At the same time, ineffective biomarkers are capable of predicting as well as monitoring patient response to MDSCs targeted therapy. This fact acts as a limitation toward personalized therapy. Finally, the complexity of clinical translation stands at a point that is one of the major current challenges and more clinical studies need to happen to verify safety and efficacy for these new therapies.

On the whole, while therapeutic approaches toward MDSCs hold promise for lung cancer immunotherapy, there are many challenges before their clinical application. In the future, more research is needed to advance a better understanding of the cross-talk mechanisms between MDSC and other immune cells, better and safe combination therapy, and more reliable biomarkers for patient selection and subsequent monitoring while offering a promise of better treatment response and prognosis for these patients. Such undertakings will position MDSC-directed therapies as one of the mainstream parts of lung cancer immunotherapy, through which lung cancer patients may achieve more desirable treatment options.

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