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Influence of Myeloid-derived Suppressor Cells in Tumor Immunotherapy

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Abstract. The immunosuppressive response of myeloid-derived suppressor cells (MDSCs) in tumor microenvironment (TME) has become an important area of tumor research. Among them, arginase 1 (ARG1), as a key immunosuppressive molecule in MDSCs, inhibits T cell function by consuming L-arginine, producing polyamines and secreting immunosuppressive cytokines, thereby promoting tumor immune escape. This article first briefly introduces the background and mechanism of action of MDSCs, and then systematically summarizes and analyzes the fine regulation of ARG1 expression by multiple factors, including transcriptional, epigenetic and post-translational mechanisms, and its specific role in MDSCs and its regulatory mechanism. Finally, the research progress of ARG1 as a potential therapeutic target is summarized, such as the development and application of ARG1 inhibitors, and the mechanisms of action and advantages and disadvantages of several different research methods are analyzed. A promising small molecule inhibitor CB-1158 and future prospects are understood, and the therapeutic direction and possible solutions for future research are proposed.

Keywords: MDSC, Immunosuppressive mechanisms, ARG1, small molecule inhibitors, CB-1158r.

1. Introduction

TME contributes greatly to the occurrence and development of cancer. The TME is composed of many kinds of cells like tumor cells, immune cells and stromal cells, it also includes a variety of cytokines and chemicals that be said to be a complex dynamic network system. TME influences the growth and spread of tumor cells, it also has a high impact on the effect of treatments. Studies have found that immunosuppressive cells such as MDSCs, regulatory T cells, and cancer-associated fibroblasts can significantly weaken the effect of immunotherapy [1]. Among them, MDSCs are a key component of the TME, and the immunosuppressive mechanism mediated by them is one of the current hot topics in tumor immunology research.

Through research, high expression of ARG1 can be regarded as one of the most typical immunosuppressive mechanisms used by MDSCs, so ARG1 is considered to be an important molecule for MDSCs-mediated immunosuppression. It exerts a powerful immunosuppressive effect by depleting L-arginine, leading to T cell dysfunction, inhibiting its proliferation and cytokine production [2]. Research on the expression and mechanism of action of ARG1 not only helps to reveal the complexity and diversity of the tumor microenvironment, but also provides new ideas and strategies for cancer immunotherapy. By understanding the methods of inhibiting ARG1 activity, small molecule inhibitors with improved pharmacokinetic properties can be developed, and other immunoregulatory pathways based on targeted L-arginine degradation control can be expanded to relieve the inhibitory influence of MDSCs on the immune system, thereby enhancing the response of anti-tumor and improving the effect of immune treatment [3].

2. Introduction of MDSCs and the Immunosuppression Mechanism

MDSCs come from myeloid precursor cells in the bone marrow. Through the action of various cytokines like GM-CSF, M-CSF, IL-6, and IL-1β, they are large-scale expanded and recruited to

tumor sites and inflammatory sites in pathological conditions like tumors, chronic inflammation, and infection [4].

MDSCs are a heterogeneous cell population, which are divided into two categories: monocytic MDSCs and granulocytic MDSCs. However, today more studies have concentrate on the affects of the immunosuppressive mechanism of MDSCs on TME, including consumption of L-arginine and generation of inhibitory metabolites, production of reactive oxygen and reactive nitrogen varieties, secretion of inhibitory cytokines, expression of immune checkpoint molecules (PD-L1, CTLA-4), lowering of local pH, and direct contact with T cells to transmit inhibitory signals. Moreover, MDSCs can also induce the generation of regulatory T cells and B cells, further enhancing the immunosuppressive effect. These combined effects weaken the effector immune cells' function of tumor inhibition and promote tumor growth and metastasis [5]. (Figure 1) Through the current experimental mouse models and clinical models, it can be concluded that MDSCs mainly exert immunosuppressive effects through high expression of ARG1, iNOS and ROS [6].

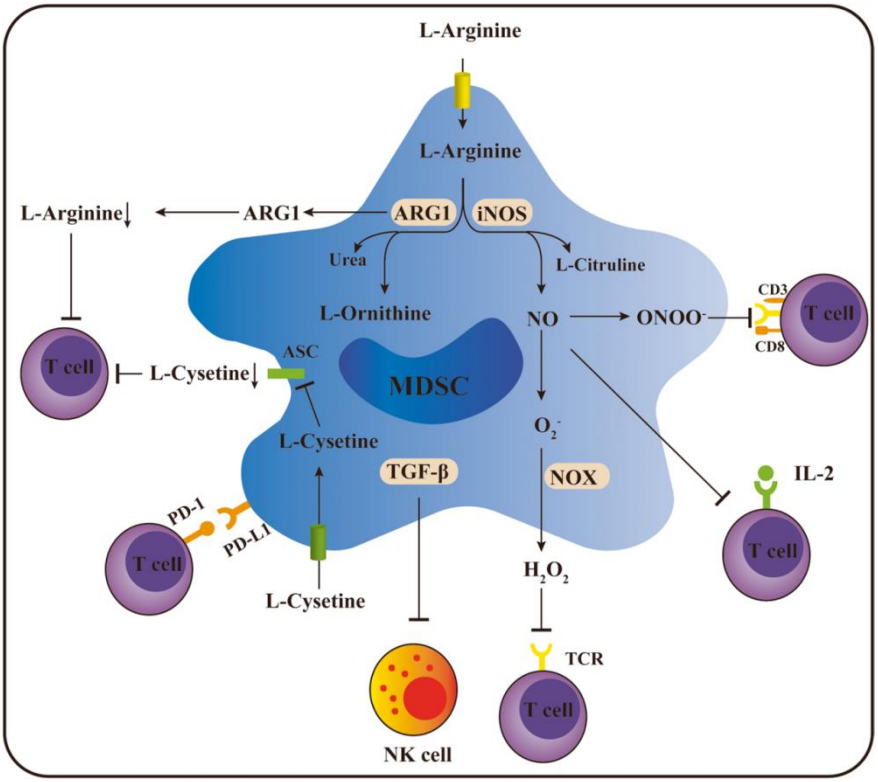

Fig. 1 Various immune escape mechanisms of MDSCs [6].

At the same time, new research is also investigating the metabolic aspects of MDSCs to uncover their biological roles. For example, a recent project used intracellular staining and sequencing to immunolabel myeloid cells expressing ARG1 in mouse tumors and to identify their molecular pathways through single-cell analysis [7].

3. ARG1 Expression and Mechanism of Action

ARG1 is composed of 322 amino acids, located in the cytoplasm, and mainly in the liver expressed . Studies have shown that the expression of ARG1 is finely regulated by multiple factors, including transcriptional, epigenetic, and post-translational regulation. In transcriptional regulation, its gene is adjusted by multiple transcription factors, like STAT6, C/EBPβ, HIF-1α, etc. These transcription factors are activated under different stimuli such as cytokines, hypoxic environment, bind to the ARG1 promoter region, and accelerate its transcription. IL-4 and IL-13 which are the main cytokines to induce ARG1 expression can increase the transcription of ARG1 by activating the STAT6 signaling pathway. IL-10 and TGF-β can also upregulate ARG1 expression through different pathways [8].

In epigenetic regulation, DNA methylation and histone acetylation status have an important influence on the transcriptional activity of the ARG1 gene. Epigenetic modification can regulate the expression of ARG1 by changing the chromatin structure [9].

The stability of ARG1 protein is also regulated by multiple factors in post-translational regulation. For example, the ubiquitination-proteasome pathway can regulate the degradation rate of ARG1 protein, thereby affecting its accumulation in cells.

Discovery through exploration，ARG1 as an enzyme can catalyze the hydrolysis of L-arginine to produce urea and L-ornithine, and L-ornithine is the substrate of ornithine decarboxylase (ODC), which can initiate the synthesis of polyamines, or be metabolized to proline by ornithine aminotransferase (OAT) [10]. L-arginine is an important amino acid for T cell proliferation and activation, and its disadvantage is that affect the restraint of effector T cells, making it difficult for T cells to grow and action [11].

In addition, Arg1 converts arginine to proline and the polyamine spermine, which better repair of tissue cells and reduce cells growth and reproduction, respectively [12]. Mechanistically, polyamines can induce cell cycle progression to make cells growth, it also provide protection against DNA damage, and prevent cells death [2]. Arginine is a key substrate needed for optimal T and NK cells to prevent the tumor [5]. Experiments have shown that compared with high arginine concentrations, the in vitro cytotoxic activity of human NK cells was obviously inhibited with low arginine concentrations, and the expression of activating receptors was reduced, and production of the interferon gamma (IFNγ) was impaired. Moreover, arginine regulates T cell metabolism by promoting oxidative phosphorylation rather than glycolysis, which in turn improves T cell survival and promotes the growth of long-lasting memory T cells with higher antitumor properties [13]. T (Figure 2). Therefore, arginine depletion by Arg1 in MDSCs can indirectly inhibit the intratumoral quantity and effect of T and NK cells, thereby inhibiting antitumor immunity [14, 15].

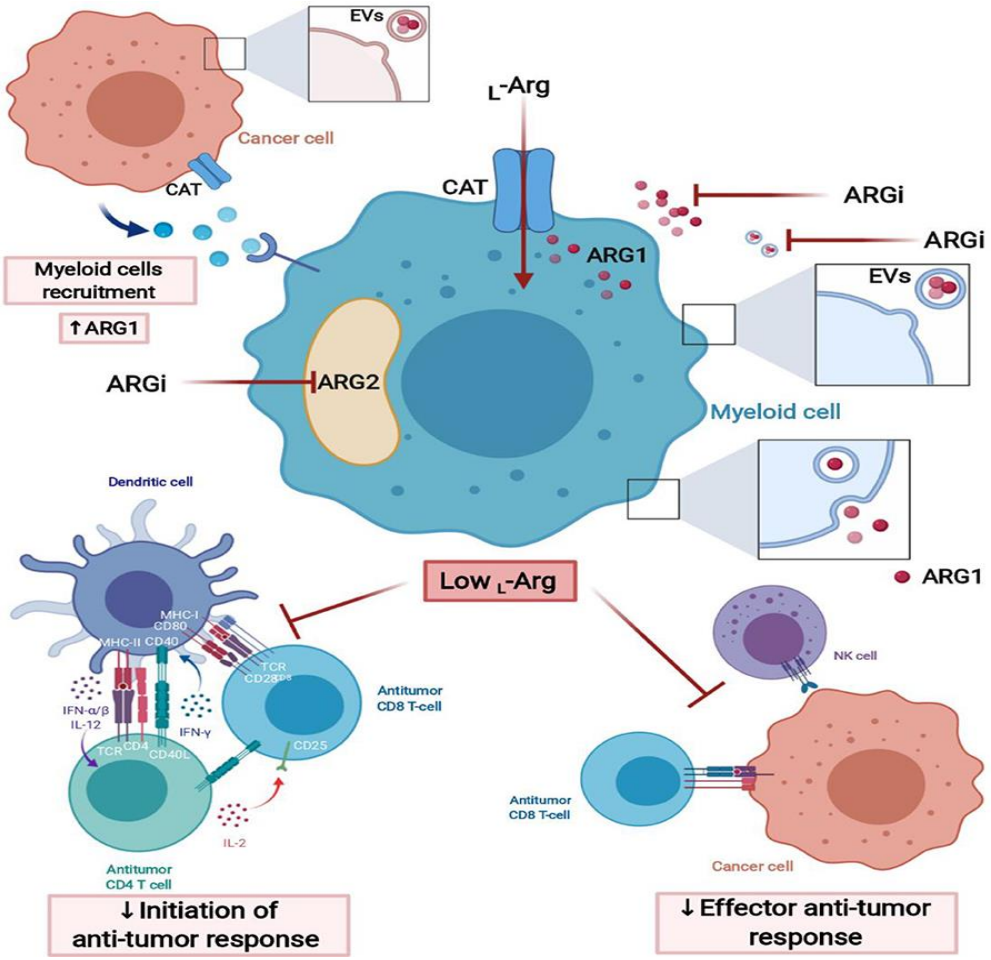

Fig. 2 The mechanism of action of L-arginine by ARG [4].

4. Exploring Methods to Inhibit ARG1

Choosing the best method to inhibit ARG1 requires consideration of different factors, such as efficacy, safety, the patient's specific condition and economic cost. Among them, there are five main methods of inhibiting ARG1 used for treatment at this stage, namely small molecule inhibitors, gene silencing technology, targeted signaling pathway inhibitors, combined immunotherapy, natural products and plant extracts. The first is small molecule inhibitors, whose mechanism is to bind to the active site of ARG1, so that ARG1 cannot bind to L-arginine and inhibit its enzyme activity. It can also inhibit ARG1, reduce the consumption of L-arginine, and increase the availability of L-arginine in the tumor microenvironment. Restoring L-arginine levels can improve the proliferation and function of T cells and NK cells [16]. Representative drugs of small molecule inhibitors include CB-1158 and others.

The mechanism of action of gene silencing technology is mainly to use small interfering RNA (siRNA) or short hairpin RNA (shRNA) to target ARG1 mRNA and reduce the expression level of ARG1 gene. At the same time, antisense oligonucleotides (ASO) can also bind to ARG1 mRNA, prevent its translation, and reduce the production of ARG1 protein. This method significantly reduces ARG1 gene expression, and can inhibit ARG1 activity for a long time, reduce the consumption of L-arginine, and improve the function of immune cells.

There are two main types of inhibitors in targeted signaling pathway inhibitors. One is the JAK/STAT3 inhibitor, which reduces ARG1 expression by inhibiting the JAK/STAT3 signaling pathway and regulates the production of immunosuppressive factors upstream. Another type is the PI3K/AKT inhibitor, which reduces the expression and activity of ARG1 by inhibiting the PI3K/AKT signaling pathway. Both inhibitors can indirectly reduce ARG1 expression, reduce the consumption of L-arginine, break away from the control of the immunosuppressive mechanism, and enhance immunity of the anti-tumor.

In combined immunotherapy, ARG1 inhibitors are used in combination with immune checkpoint inhibitors PD-1/PD-L1 antibodies to enhance T and NK cells function by relieving multiple immunosuppressive pathways. There are also cancer vaccines and CAR-T cell immunotherapies. ARG1 inhibitors are used in combination with these immunotherapies to further activate the immune system and improve the anti-tumor effect. This approach can significantly improve the therapeutic effect, promote the overall anti-tumor immune response, and is applicable to a variety of tumor types.

Natural products and plant extracts have low bioavailability and may require improved delivery systems. They are less used than other methods, but they are safer and have multiple biological activities. Among them, curcumin can inhibit ARG1 activity through multiple pathways and reduce the consumption of L-arginine. Resveratrol can also indirectly inhibit the expression and activity of ARG1 through antioxidant and anti-inflammatory effects [10].

Each method of inhibiting ARG1 has its own unique mechanism of action and advantages and disadvantages. For example, although small molecule inhibitors are highly specific and can directly act on ARG1 enzyme activity, and preclinical studies are relatively in-depth, they require high doses to maintain and can cause side effects. The delivery system of gene silencing technology is complex, easily causing immune responses, and has high technical requirements and high costs. The advantage of combined immunotherapy is that it has a synergistic effect and is applicable to a variety of tumor types, but it also increases the risk of side effects. Therefore, for the selection of various methods, it is necessary to understand the specific clinical situation and individual differences.

5. CB-1158 Drug Research

As a highly effective and selective ARG1 inhibitor, CB-1158 has shown good prospects in clinical applications, especially when used as a single drug in combination with immune checkpoint inhibitors

or other therapies to stop tumor growth in the same model, which is a method that is currently being studied in depth [17].

The effects of CB-1158 can be obtained through various experiments. In mouse tumor models which have same gene, CB-1158 transferred the tumor immune landscape to a proinflammatory TME. In addition, through the study of tumor microenvironment, it shows that the expression of tumor-infiltrating CD8+ T cells and NK cells, inflammatory cytokines, and interferon-induced genes can be increased by the CB-1158，thereby improving the efficacy of drugs which can suppress the cancer such as gemcitabine, immune checkpoint antibodies, adoptive T cell therapy, and stop the tumor from growing. CB-1158 now develop many clinical experiments for patients who have solid tumor malignancies [18].

In addition, much research data can be see that CB-1158, as a small molecule inhibitor that directly inhibits ARG1 enzyme activity, has displayed very good anti-tumor curative effect and safety in preclinical and early clinical trials. The clinical research prospects of CB-1158 can expand its indications. Future studies will explore the application of CB-1158 in more tumor types, especially those that are insensitive to traditional treatments. The dosing regimen can also be optimized. Further dose optimization studies and pharmacokinetic studies will help determine the best dosing regimen, improve therapeutic effects and reduce side effects. At the same time, the biomarkers of CB-1158 can be studied, predictive biomarkers can be identified and verified, and the patient groups most possible to respond to CB-1158 treatment can be screened to achieve personalized treatment [19].

6. Conclusion

MDSCs are a type of cell population that have an vital immunosuppressive effect in the tumor microenvironment and ARG1 is key of the immunosuppressive mechanism in these cells. It can control the function of effector T and NK cells by consuming L-arginine, promoting tumor immune escape and progression. Small molecule inhibitors targeting ARG1, such as CB-1158, can restore L-arginine levels and enhance T cell function, becoming an effective anti-tumor treatment strategy. Future research will further optimize these treatments, improve anti-tumor effects, and bring more hope to patients.

In addition, studying new targeted molecules and pathways and finding more mechanisms for regulating MDSCs and ARG1 will provide a basis for the production of various therapeutic drugs. Study on the formulation of personalized treatment plans based on patient-specific tumor types, immune microenvironments, and gene expression profiles will make treatment more precise and effective. In short, through multi-faceted research and clinical practice, targeted therapy for MDSCs and ARG1 will be increasingly important in the fight against cancer later, bringing hope of recovery to more patients.

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