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Enhancing the Effect of PD-1/L1 Blockers by Polarizing M2 Tumor-associated Macrophages (TAMs)

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Abstract. The cancerous microcosm, known as the tumor micro-environment (TME), encompasses a highly intricate network where a multitude of cells and their emitted substances significantly contribute to the development and advancement of malignant growths. The role of TAMs in the TME has been increasingly valued. Owing to its significant plasticity, it typically divides into pro-inflammatory M1 and anti-inflammatory M2. Within TME, TAMs typically show polarization towards M2. Antibodies are used by PD-1/L1 blockers to prevent PD-1 and PD-L1 from binding, aiming to reduce tumor symptoms. Presently, the efficacy of this medication is limited to a select few patients, in contrast to other patients who exhibit a level of resistance to the drug. Latest research indicates that M2 TAMs exert a suppressive influence on the PD-1/L1 blockade treatment. This substance suppresses the growth and penetration of CD8+T cells and generates Indole 2,3-dioxygenase (IDO), resulting in resistance to PD-1/L1 inhibitors and facilitating the multiplication and evasion of cancer cells. Some studies have reduced the resistance to PD-1/L1 blockers and promoted the treatment of tumors by polarizing TAMs. The dissertation compiles identified TAMs polarization routes and the impact of M2 TAMs on PD-1/L1 inhibitors. The discussion also encompasses present-day techniques for directing M2 TAMs towards the M1 type and advocating these approaches on PD-1/L1 blockers.

Keywords: Tumor-associated macrophages (TAMs); PD-1/PD-L1; Tumor micro-environment (TME); Macrophage polarization; PD-1/L1 blockers.

1. Introduction

Investigating the Tumor micro-environment (TME) is recognized as highly beneficial in cancer research. Numerous signal factors and immune cells play a significant role in the expansion of tumors. Within this group, tumor-associated macrophages (TAMs) constitute a significant portion of immune cells and play a crucial role in TME. These elements are crucial in various cancers, including gastric (GC), liver (LC), and breast (BC) cancers. For instance, TAMs are known to emit CCL2, IL-1α, IL-6, and TNF-α, which directly stimulate the growth of cancer cells; promote tumor metastasis; inhibit T cell function, etc, and a substantial quantity of TAMs is typically viewed as an unfavorable prognosis. TAMs have high plasticity. According to the expression of surface receptors, secreted substances, metabolic methods, and specific functions, macrophages can be classified into multiple phenotypes. However, in general they can be divided into the classically activated M1 phenotype and the alternatively activated M2 phenotype. Both phenotypes are polarized from M0 macrophages, and there are also many "intermediate" macrophages that have both anti-inflammatory and pro-inflammatory effects. Due to their high plasticity, the surrounding environment's manipulation of their polarization cannot be ignored. Among macrophages, the polarization of TAMs is largely controlled by cancer cells. M1 TAMs are very important cells in tumor suppression. They can present surface antigens to T cell receptors (TCRs) and release chemokines. Additionally, they are capable of triggering type I T cell reactions through the expression of IL-12/23 and generating pro-inflammatory agents like IL-1, TNF-a, and NO [1], and recruit CD8+T cells or NK cells into the TME. M2 TAMs are the "accomplices" of tumor cells. By inhibiting M2 TAMs, tumor cells release anti-inflammatory agents like IL-10, TGF-β, and IL-1 receptor antigen (IL-1RA), aiding their growth, fostering angiogenesis, tissue restructuring, and repair, thereby diminishing immune reactions [1]. Certain elements within the tumor microenvironment are capable of emitting M2-polarizing

cytokines, including interleukin-10, a range of CCL2 to CCL8, CXCL12, vascular endothelial growth stimulator, as well as platelet-derived growth factor (PDGF), which serve to attract additional monocytes and naive M0 macrophages to the site, subsequently driving their differentiation into M2-type tumor-associated macrophages. [2]

Typically, CD8+ T lymphocytes, serving as pivotal cells within the immune system's suppressive pathway, are capable of averting autoimmune reactions by sustaining immunological tolerance and modulating the immune response's magnitude. Yet, within the TME, tumors elude the immune monitoring of CD8+T cells by manifesting PD-L1. Known as the "checkpoint", this process may diminish the immunological strength of CD8+T cells and lessen their suppressive impact on tumors. Immunotherapy targeting PD-1/PD-L1 blockade has demonstrated significant benefits in extending the lifespan of individuals with diverse tumors, including lung cancer [3], GC [4] and BC [5]. For example, nivolumab, pembrolizumab and atezolizumab have been developed and used [6]. They can prevent the activation of this pathway by binding to PD-1 and PD-L1 in advance. However, PD-1/L1 blockers are currently only effective in a small number of cancer patients [7]. Tumors in other cancer patients are resistant to this type of drug. Current studies have shown that M2 TAMs are largely responsible for the resistance to PD-1/PD-L1 blocking antibodies. [8] As an illustration, tumor cells suppress CD8+ through the release of granulin or various signal factors, while T cells M2 TAMs reduce the engagement, penetration, and multiplication of CD8+T cell activities. (The mechanism of how this substance increases resistance to PD-1/L1 blockers is still unknown, but it has been confirmed that the presence of IDO would have an inhibitory effect on PD8+ [9])

Therefore, PD-1/L1 also has great application value in cancer treatment, and can be used with polarizing drugs of different M1 TAMs. This thesis discusses the mechanism of action of TAMs polarization, the effect on PD-1/L1 blocker resistance and the effect of current polarization methods when used together with PD-1/L1.

2. TAMs Polarization

TAMs have two main sources: circulating monocytes in the bone marrow and resident macrophages in the embryo. Although there are a certain number of TAMs transformed from embryonic macrophages in the TME, studies have shown that the plasticity of this cell is poor [10]. Therefore, this thesis only explains TAMs transformed from circulating monocytes in the bone marrow.

During the initial phase of a tumor, the M1 component in TAMs holds a predominant role. However, as tumor cells develop to maturity, TME gradually "holds" this process, polarizing M1 TAMs into M2 TAMs. This process is very complicated, and many studies have found the related polarization effects in different signal pathways.

2.1. External Polarization

The main polarization mode of TAMs is external polarization. After monocytes or MO TAMs are recruited to the TME due to factors such as high concentrations of chemokines [11], signal factors secreted by certain cells (such as CD4+TH1/TH2 cells) can mediate them into M1 or M2 TAMs. For instance, the action of IFN-γ triggers the activation of STAT1, leading TAMs to produce genes associated with M1 phenotype; conversely, both IL-4 and IL-13 stimulate STAT6, prompting TAMs to manifest genes tied to the M2 phenotype; moreover, the AKT/mTOR signaling cascade facilitates macrophage-originated TAMs to suppress the progression of TAMs towards the M2 pathway. (Refer to Figure 1 for a detailed illustration). Some non-cytokine substances can also affect the polarization of TAMs, such as hypoxia, intratumoral lactic acid, etc. [12]

2.2. Hypoxic Polarization

In addition to external polarization, hypoxia is also an important possible factor in polarizing M2 TAMs. Within the tumor microenvironment, persistent oxygen deprivation and cell death adjacent to neoplastic cells result in the secretion of high mobility group box 1 protein (HMGB1). The level of

this molecule's manifestation is intricately linked to the progression of malignancies, including hepatocellular carcinoma (HCC) [13], colon cancer [14], etc. Some studies have analyzed the in vitro melanoma model by flow cytometry and found that a large number of M2 TAMs were expressed in the HMGB1-positive model [15]. Various research endeavors have highlighted that an oxygen-depleted milieu has the capacity to react to endoplasmic reticulum distress and reactive oxygen species-mediated stress, triggering a similar reaction that results in the differentiation of TAMs [16]. Because M1 and M2 have different metabolic types, hypoxia is a very important polarizing factor (Figure 1).

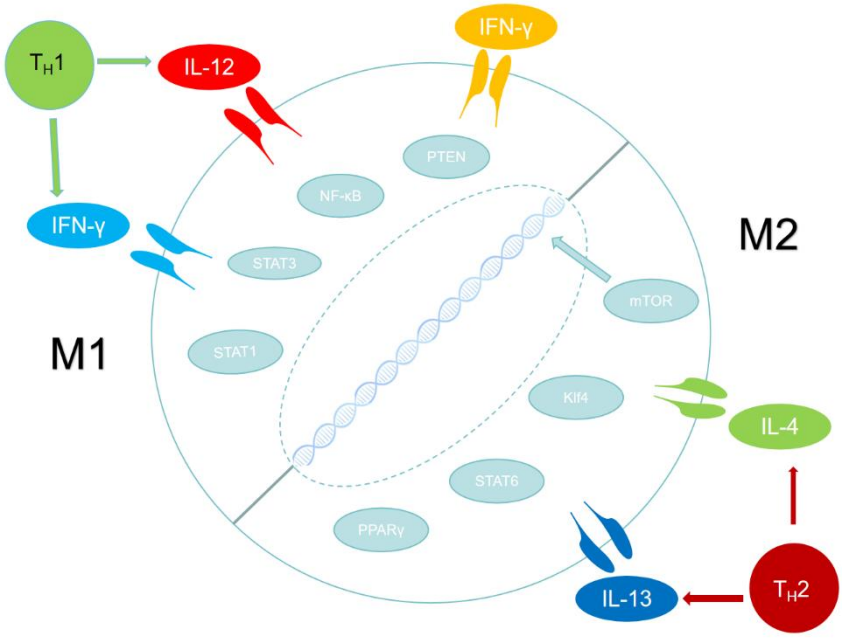

Fig. 1 Pathways for TAMs Polarization by TH1/TH2.

3. PD-1/L1 Blockers

3.1. Principle of Blockers

PD-1 is an important target on CD8+ cytotoxic T cells. The primary purpose of this mechanism is to shield neighboring cells from the detrimental effects of overly aggressive pro-inflammatory reactions. Utilizing this characteristic, tumors manifest PD-L1 ligands either on the body's exterior or within certain immune cells in the Tumor Microenvironment. The binding of the PD-1 ligand to PD-1 on CD8+T cell surfaces hinders their TCR, rendering them incapable of tumor destruction and potentially leading to T cell depletion.

In contrast to alternative therapies like chemotherapy, immunotherapy boasts elevated levels of responsiveness, remission, and survival odds [17]. The FDA has given the green light to six inhibitors targeting PD-1 and L1 for the management of non-small cell lung carcinoma. Yet, the efficacy of PD-1/L1 inhibitory treatment is confines itself to a narrow spectrum within the cancer domain, with the incidence of patients responding favorably to the medication not surpassing 40%. Despite a subset of patients encountering a measure of regression, a significant portion eventually succumbs to medication-resistant mutations and continues to face disease advancement [18].

3.2. Attenuation of Blocker Effects Caused by TAMs

3.2.1. Prevent CD8+ recruitment and infiltration

There is evidence that CD8 T cell trafficking to tumors requires the CXCR3-CXCL9/CXCL10 axis [19]. Peranzoni et al. [20] discovered that inhibiting CSF-1 (the signal for TAMs recruitment) led to an enhancement in the infiltration capabilities of CD8+ T cells within the TME and an increase in the

effectiveness of PD-1 inhibitors. Hence, it is conjectured that M2 TAMs diminish the efficacy of PD-1/L1 inhibitors through the attenuation of CD8+ T cell accumulation and penetration within the tumor microenvironment. Interestingly, there are indeed studies reporting that TAMs and tumors produce galectin-3, which reduces the expression of CXCL9 and CXCL10 [21], but this experiment did not further verify whether this substance is the main reason for the difficulty in recruiting and infiltrating CD8+T cells.

3.2.2. Release IDO and prevent CD8 + activation

According to Yu Yuan et al. [22] found that M2 TAMs can promote tumor release of indole 2,3-dioxygenase (IDO), which can enhance the activity of Tregs and MDSCs, thereby inhibiting CD8+T cell activity and increasing PD-L1 resistance (See Figure 2 for details). M2 TAMs can also produce IDO themselves, and the IDO they secrete can even polarize M1 TAMs to M2 type, further leading to PD-1/L1 blockade resistance [23].

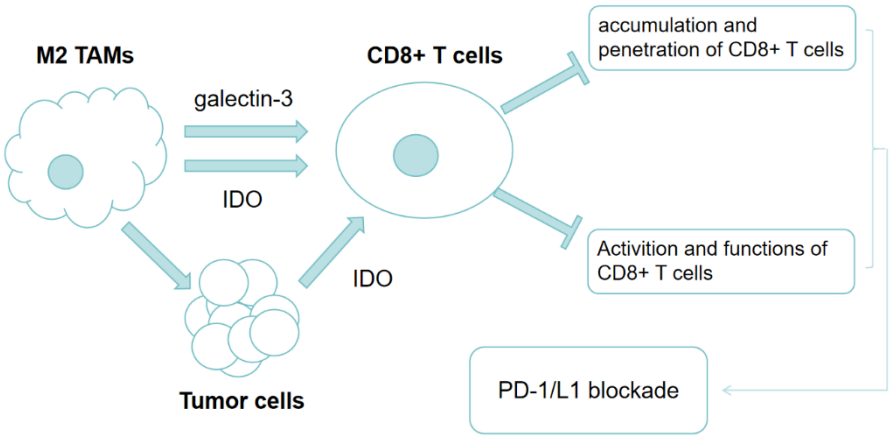

Fig. 2 Key mechanisms of PD-L1 resistance

4. M1 TAMs Polarization Strategy

This thesis classifies the treatment of polarised TAMs into three methods by principle of action and method of drug delivery (See Figure 2 for details). The following drugs have all been shown to polarise TAMs to the M1 type and have a promoting effect on PD-1/L1 blockers (Table 1).

Table 1. TAMs polarizing drugs and their specific contents

References	Name	Year	Tumor type used in the experiment	Strategy	Additional tumor-killing capacity	M1 polarization mode
[24]	Rapamycin (R), hydroxychloroquine (Q)	2020	Glioblastoma	Combined PD-1 blocker use	Improve the phagocytosis ability of macrophages	Inhibition lipid metabolism
[23]	α-T-K	2021	Lung cancer	Combined PD-1 blocker use	Without	ER stress-related IRE1-XBP1 pathway, ROS pathway
[25]	Vinblastine	2023	MC38	Combined PD-1 blocker use	Improving phagocytic ability and cytotoxicity of phagocytic cells	Upregulation of the NF-κB-Cyba-ROS pathway
[26]	MPW or C-MPW (modified polysaccharide) combined with doxorubicin (Dox)	2020	4T1	Chemotherapy and immunotherapy	Has stronger anti-tumor effect than chemotherapy, reduces systemic toxicity and inhibits tumor metastasis	NF-κB and STAT1 pathways are up-regulated and STAT3 pathway is down-regulated
[27]	Regorafenib	2020	HCC	Combined PD-1/L1 blocker use	Anti-tumor angiogenesis	Downregulation of p38MAPK/Creb1/Klf4 signal pathway
[28]	(anti-MS4A4A)	2023	Rectal cancer	Combined PD-1 blocker use	Inhibition of tumor growth	Downregulation of PI3K/Akt/mTOR and JAK/STAT6
[29]	Man@pSiNPs-erastin	2022	HCC	Encapsulation with Met@Man nanopthesiss followed by combined PF-L1 blocker use	Inhibition of tumor growth by ferroptosis	SOCS3-STAT6-PPAR-r pathway inhibition. The reactivity of TAMs to IL-4 is reduced.
[30]	CDNP-R848	2018	MC38	Encapsulation with cyclodextrin nanopthesiss (CDNP) followed by combined PD-1 blocker use	Without	TLR7/8-NF-κB pathway upregulation

[31]	Met@Man-MPs	2021	H22, 4T1, colon cancer models	Encapsulation with Met@Man nanopthesiss followed by combined PF-1/L1 blocker use	Improve the cytotoxicity of TAMs and enhance their phagocytic ability to degrade tumor collagen (ECM).	Upregulating the AMPK signal pathway

4.1. Cellular Metabolic Strategies

4.1.1. Rapamycin (R), hydroxychloroquine (Q)

When used in combination, rapamycin (R) and hydroxychloroquine (Q) act as mTOR inhibitors to reduce the fatty acid metabolism capacity of macrophages, thereby polarizing some TAMs toward the M1 type of glycolytic metabolism, while reducing the number of M2 macrophages. Since tumor cells have a high demand for cholesterol, inhibiting cholesterol metabolism can weaken the ability of tumor cells to attract macrophages, thereby reducing the number of TAMs. This experiment combined RQ with PD-1 blockers for immunotherapy of GBM, and the results showed a significant enhancement effect. The findings further illustrated that RQ boosts the engulfing capacity of macrophages, thereby elevating the engulfing potential of TAMs as it prompts these cells to accumulate fat droplets [32]. and inhibiting the CD47-SIRPα pathway (macrophage phagocytosis inhibition pathway), which is also one of the advantages of this treatment method.

4.1.2. α-T-K

From a metabolic perspective, due to the frequent interruption of the tricarboxylic acid cycle, the metabolic type of M1 TAMs is mainly glycolysis, while that of M2 is oxidative phosphorylation and fat phosphorylation [33]. Under hypoxic conditions, endoplasmic reticulum stress activates the IRE1-XBP1 pathway, resulting in the inhibition of glycolysis, while oxidative phosphorylation and fat phosphorylation are promoted,caused TAM to polarize to M2. α-TK (containing the endoplasmic reticulum stress inhibitor KIRA6, hereinafter referred to as α-TK) can inhibit endoplasmic reticulum stress and the M2 polarization direction, and promote cell polarization to M1. ROS in the oxidative metabolic pathway promotes TAMs to M2 polarization by promoting the ERK-STAT6 pathway. As an antioxidant, α-TK can remove ROS and promote cell polarization to M1. α-TK can be taken up by TAMs, has targeted properties. As an antioxidant, it has high safety.

4.2. Inflammatory Pathway Strategy

4.2.1. Vinblastine

Vinblastine (VBL) upregulates the expression of Cyba, leading to increased production of ROS, which further polarizes TAMs into M1-like phenotypes. In TAMs, VBL enhances the NF-κB-Cyba pathway, which can control the secretion of IL-12+IFNγ by TAMs. These two factors can allow CD8+T cells to proliferate and activate themselves. ROS formed by P22phox, a key protein encoded by Cyba, plays a role in polarizing TAMs. Research revealed that employing N-acetylcysteamine (NAC) for ROS elimination notably diminished macrophages' growth impact on CD8+T cells, suggesting the NF-κB-Cyba-ROS axis as a crucial route for TAM polarization and CD8+T cell activation. As per the previously referenced α-TK medication regimen [23], In macrophages, ROS is involved in effects that are both inflammatory and anti-inflammatory. In this study, triggering the NF-κB-Cyba-ROS pathway increases the likelihood of ROS exhibiting pro-inflammatory properties. Some studies have shown [34] that inhibiting ROS in monocytes can prevent cells from polarizing to the M2 type. VBL can play a certain role in preventing monocytes in the TME from differentiating into TAMs.

Another finding is that a study [35] used three microtubule-targeting drugs (MTAs) including colchicine, paclitaxel and VBL to polarize M2 TAMs. All three groups were polarized to M1.

Interestingly, only the VBL-treated group promoted the PD-1 blocker, while the other two groups still showed drug resistance. It showed that polarizing TAMs to M1 may not necessarily promote the effect of the blocker. Compared with the first two, the phagocytic ability of TAMs treated with VBL was also improved. The thesis believed that this is caused by VBL increasing the lysosomal activation of TAMs. For general TAMs, their phagocytic ability is generally not very strong. Combined with the effect of RQ mentioned above, whether the ability of polarized TAMs to promote PD-1/L1 blockade is related to their phagocytic ability or lipid metabolism ability is also a question that can be discussed.

4.2.2. MPW or C-MPW in combination with doxorubicin

MPW was used in combination with C-MPW with enhanced immunomodulation modified by cationization and Dox. Upon application in 4T1 mice, the medication demonstrated a more potent anti-cancer impact compared to Dox by itself. Crucially, the research revealed MPW and C-MPW's ability to control NF-κB, STAT1, and STAT3 signaling routes, categorize TAMs into M1 types, and enhance the release of IL-12, TNF-α, and INF-γ. Reactivates the immune system in TME such as CD8+T cells. However, compared with the first two treatments, this experiment did not use PD-1/L1 in combination. Based on the above experiments, observations reveal that directing M2-type TAMs towards M1-type TAMs doesn't invariably amplify the impact of PD-1/L1 blockers.However, because the signal pathways regulated by MPW and C-MPW polarized TAMs and the signal factors produced by M1 TAMs after polarization have a high degree of coincidence with RQ and VBL, this thesis speculates that this drug can be combined with PD-1/L1 blocking agents.

4.2.3. Regorafenib

Regorafenib is used as a second-line medical drug in advanced liver cancer, colorectal cancer, and GC. The main effect was thought to be anti-angiogenic in the past. However, this experiment suggests that Regorafenib mainly inhibits M2 TAMs polarization by down-regulating the p38MAPK/Creb1/Klf4 signal pathway, while M1 macrophages activate T cell proliferation to increase immune response. The drug Anti-PD-1 was administered alongside Regorafenib. Relative to the sole use of anti-PD-1, this treatment markedly reduces tumor expansion and enhances mouse survival rates.

4.2.4. Anti-MS4A4A mAb

The MS4A4A gene is capable of prompting TAMs to produce an extensive array of M2 antibodies, including CD163, VEGFA, IL-10, ARG1, TGFB1, and others, while inhibiting MS4A4A can increase the reproduction efficiency of CD8+T cells. The distinct process involves MS4A4A guiding TAM polarization through the regulation of the PI3K/Akt/mTOR and JAK/STAT6 signaling routes. Anti-MS4A4A antibody mAb was used in combination with PD-1 blocker. The results showed that the antibody can repolarize TAMs into M1 type by inhibiting the MS4A4A gene and increase the effect of PD-1 blocker by activating CD8 +.

4.3. Nanopthesis Targeting Strategies

4.3.1. Nanopthesis targeted xCT

xCT (encoded by SLC7A11) was found to be upregulated in a variety of TMEs [36,37]. The function of this protein is to control glutathione and antioxidants. The heightened expression of SLC7A11 fosters tumor development through the suppression of ferroptosis [37], and xCT is a very important substance in this process. The study concluded that xCT's existence enhanced macrophage penetration into the TME. TAMs expressing xCT were more likely to cause tumor metastasis. In the end, they found that xCT can control the polarization of TAMs to M2, thereby promoting tumor development. xCT can upregulate the SOCS3-STAT6-PPAR-r pathway to make TAMs express more M2 characteristic proteins. By knocking out the xCT expression gene, it was found that the expression of IL-4 upstream of the pathway was not inhibited, but TAMs were difficult to respond to IL-4. This may be the mechanism by which xCT mediates the polarization of TAMs.

The erastin and GPx4 (peroxidoreductase, inhibiting ferroptosis) inhibitor RSL3 are often used to promote ferroptosis, but ferroptosis is not exclusive to TAMs, not an apoptotic program. Direct use of such drugs may "accidentally injure" other cells in the body. Therefore, this experiment uses nanopthesis mannose Man@pSiNPs targeting M2 TAMs to perform targeted therapy on TAMs. The study also integrated the combined effects of PD-L1 blockers, discovering their synergistic action in diminishing TAM infiltration and boosting CD8+T cell activity.

Surprisingly, this experiment found that TAMs without xCT would express more PD-L1 and bind to blockers. This is used to explain the enhancement of polarized TAMs on PD-L1. Some studies have pointed out that M2-type TAMs express a large amount of PD-L1, while M1-type TAMs express very little. [38] This undoubtedly contradicts the conclusion of this experiment. This article speculates that xCT does cause the polarization of TAMs, but this pathway also inhibits the expression of PD-L1. After inhibiting xCT, TAMs were polarized to M1 type, but the expression of PD-L1 would also increase, so this method could enhance the effect of PD-L blockers

Inhibition of xCT can also promote the ferroptosis of TAMs through GPX4/RRM2 signaling regulation, thereby inhibiting the invasion of TAMs into tumors. However, its correlation with TAMs polarization has not been found so far.

4.3.2. CDNP-R848

R848 acts as an agonist for TLR7/8. This entity has the ability to attach to TLR7/8 in a laboratory setting, triggering the NF-κB pathway and thus effectively transforming M2 TAMs into M1. However, TRL agonists cause symptoms such as headache and fever when administered systemically, so they cannot be administered systemically repeatedly [39]. Targeted therapy can alleviate this symptom, and its effect is similar to the encapsulation therapy used in chemotherapy. It is known that dextran nanopthesiss have macrophage tropism, which also allows macrophages to quickly aggregate in the TME to form TAMs. β-cyclodextrin (CD) has a chemical composition similar to dextran. It is synthesized with L-lysine into cyclodextrin nanopthesiss (CDNPs), which encapsulate P848 for targeted therapy of TAMs. In colon cancer, the combination of CDNP-R848 and PD-1 blockers can enhance its effect. In melanoma that does not respond to PD-1 blockers, the combination of the two also shows a certain therapeutic effect.

4.3.3. Met@Man-MPs

Medication Metformin (abbreviated as Met) serves as a therapeutic agent for managing diabetes and demonstrates anti-tumor properties. Its mechanisms include modulating the metabolic processes of tumors, obstructing the progression of the tumor cell cycle, suppressing the formation of new blood vessels in tumors, and eliminating cancer stem cells through the activation of adenosine monophosphate kinase (AMPK). MPs, which are extracellular vesicles produced by cells measuring 100-1000 nm in diameter, possess distinctive characteristics such as the transfer of messenger molecules, enzymes, and genetic substances (DNA, RNA) among cells, along with superior circulation stability, high biocompatibility, reduced immunogenicity, and toxicity.

By enhancing the AMPK signal pathway, Man-MPs steered M2 TAMs towards the M1 type. In this timeframe, there was an increase in the activity and penetration of CD8+T cells. The medication was mixed with the previously mentioned nanopthesiss-targeting M2 TAMs. Mannose-modified macrophage-derived micropthesiss constituted the targeted drug Met@Man-MPs, and the combination of PD-1 blockers showed that the inhibitory effect on tumors was significantly improved. Man-MPs also show MMPs activity, which can digest tumor collagen (ECM). Tumor ECM can block drugs such as PD-1 blockers from approaching tumors, weakening the effect of such drugs. Following the alleviation of the tumor's extracellular matrix (ECM), the presence of CD8 + and the enhancing impact of PD-1 blockers were observed. The targeted drug improves the effect of PD-1 blockers in two directions. This thesis believes that the drug has great potential in future clinical aspects.

5. Conclusion

In this thesis, the strategies for polarizing TAMs are roughly divided into three types. The initial objective involves diminishing TAMs' supportive role on cancer cells and aligning them with the M1 type through macrophage metabolism regulation. Both the second and third are through inflammatory signal pathways, directly polarizing TAMs and performing other functions. The third type uses more efficient and safer nanopthesis targeted therapy, using nanopthesiss that are harmless to cells to carry the required drugs, which can greatly increase the efficacy and reduce side effects. The nanopthesiss targeting TAMs are mannose-modified macrophage derivatives, and cyclodextrin (CD) with macrophage tropism combined with L-lysine to form nanopthesiss (CPNPs). All of the above methods can efficiently polarize M2 TAMs to M1 type.

However, the current studies basically stop at whether M1 TAMs activate CD8+T cells, but have not clearly explained the specific activation mechanism of CD8+T cells by M1. This paper explores the phenomenon beyond the impairment of T cells due to granin and IDO, revealing that the stimulation of T cells by M1 TAMs appears to be connected with the lysosomal compartment. These specific activation mechanisms, including the subsequent promotion mechanism of M1 for PD-1/L1 blockers, are still full of mysteries.

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