

Mechanisms of SPP1⁺/TREM2⁺ Tumor-Associated Macrophages in Immunotherapy Resistance and Combined Targeted Therapy Strategies

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Abstract

Immunotherapy resistance in solid tumors is closely related to multi-level immunosuppression in the tumor microenvironment (TME), with tumor-associated macrophages (TAMs) playing a central role. This review summarizes the heterogeneity of TAMs and their interactions with cancer-associated fibroblasts (CAFs) and lactate metabolism, focusing on the mechanisms by which SPP1⁺ and TREM2⁺ TAMs mediate immunosuppression, matrix remodeling, and metabolic adaptation. SPP1⁺ TAMs can promote CD8⁺ T cell exhaustion and form a positive feedback loop with CAFs, while TREM2⁺ TAMs enhance immunosuppression through pathways such as PI3K/Akt/mTOR and NF-κB/STAT1. The CXCL9⁺/SPP1⁺ TAM ratio may serve as a potential biomarker for predicting immunotherapy response. Existing research indicates that targeting TAMs alone has limited efficacy, and combining them with immune checkpoint inhibitors and matrix and metabolic modulators may be more effective. Future research should strengthen biomarker-driven patient stratification and explore combined strategies such as lactate metabolism and epigenetic regulation to improve the response of "cold" tumors to immunotherapy.

Key words

Tumor-associated macrophages; SPP1; TREM2; Cancer-associated fibroblasts; Lactate metabolism.

1. Introduction

Tumor-associated macrophages (TAMs) are core

myeloid components of the tumor microenvironment (TME), which are reprogrammed by cancer cells and stromal signals, and are mostly biased toward a tumor

promoting phenotype. TAMs remodel the extracellular matrix by secreting cytokines and proteases, drive angiogenesis, immunosuppression, tumor invasion and metastasis, and mediate chemoradiotherapy and immune checkpoint therapy resistance. They are key targets for targeted remodeling of the TME.

Single cell sequencing confirmed that TAMs are a continuous functional lineage rather than a single M1 / m2 subtype, and TAMs have two origins; Tissue resident macrophages (TRMS), circulating monocyte derived macrophages (TAMs, monocytes reprogrammed into tumor promoting TAMs in the TME). TAMs can be divided into multiple subgroups, such as SPP1 +, CXCL9 +, TREM2 +, and each subgroup has high heterogeneity and interconvertible plasticity, which is the biggest obstacle to the clinical transformation of macrophage targeted drugs [1,2].

Spp1+ TAMs are mainly mononuclear and highly plastic. Its core tumor promoting and immune resistance mechanisms are divided into three modules, including interacting with CAFs to construct fibrotic immune rejection, mediating ICI resistance to directly deplete CD8 + T, and driving epithelial mesenchymal transition (EMT), angiogenesis, and constructing a pre metastatic microenvironment (PMN). Only clearing the existing spp1+ macrophages, the continuous secretion of lactate and chemokines by cancer associated fibroblasts (CAF) will drive mononuclear / intermediate macrophages to rapidly differentiate into new inhibitory subtypes and form drug resistance; Based on this compensatory escape mechanism, multiple combination treatment strategies were gradually implemented: immune checkpoint inhibitors (pd-1/pd-11) combined with CAF targeted drugs (anti FAP, TGF β inhibitors), SPP1 targeted molecular drugs (anti-spp1 neutralizing antibody, nilotinib, quercetin, denosumab) combined with PD-1 inhibitors and ciferadenant combined with PD-L1 inhibitors showed good therapeutic prospects [3-5].

TREM2 + TAMs are almost all derived from circulating Ly6C + monocytes, and their trem2-stat3 pathway directly activates SPP1 transcription, which often co expresses with SPP1 to form a dual immune barrier; TREM2 + myeloid cells mediate multiple immunosuppressive mechanisms; It can directly inhibit adaptive immunity, regulate myeloid suppressor cells, and interact with CAFs to build a pro metastatic microenvironment.

When only the TREM2 + subpopulation is cleared, the monocytes will compensatory differentiate into SPP1 + macrophages, and there is Tam plastic escape. Based on the immune resistance compensation mechanism of the mutual transformation of macrophage subsets, combination therapies such as engineered mab17, fucose depleted enhanced anti-trem2 antibody combined with PD-1, bispecific antibody PD-1 $\times$ TREM2 scFv, multi-pathway combination (TREM2 inhibitor + lactate metabolism inhibitor + PD-1), and innovative drug mite-144 show good therapeutic prospects [6-8].

CAFs secrete lactic acid through aerobic glycolysis, which acts as a key signaling molecule in the TME and is involved in initiating and continuously driving the metabolic reprogramming of cancer cells. CAFs also work with TAMs to build a microenvironment of immunosuppression and tumor progression by secreting soluble factors, protein interactions, multi-level regulation of mononuclear recruitment through the complement pathway, Tam survival and tumor promoting reprogramming. At present, therapeutic targets targeting the caf-tam stromal loop have been developed for this mechanism, and the combined strategy: simultaneously blocking CAF chemokine secretion and Tam lipid metabolism pathway has a good prospect in relieving dual immunosuppression [7,9].

In the apparent positive feedback pathway of lactate-trem2-spp1, lactate is also a key signal to activate CAFs and promote the reprogramming of immunosuppressive tumor promoting TAMs. In the TME, TREM2 promotes glycolysis and generates a large amount of lactate. Lactate and histone lactation form a positive feedback loop, which cooperatively up regulates SPP1 and jointly mediates primary drug resistance at immune checkpoints. Studies have proved that dual combination therapy such as CAF stromal pathway (CXCL12, IL6, FAP) inhibitors plus lactate apparent pathway (mct/ldha/ p300 lactate transferase) inhibitors fx11 + metformin has a good therapeutic prospect [10,11].

This article focuses on two kinds of tumor promoting macrophage subpopulations, SPP1 + and TREM2 + to explain their positive feedback loop with CAF and lactate and compensatory drug resistance mechanism, and sort out the multi-target combined immunization scheme. The aim is to clarify the molecular mechanism of macrophage heterogeneity mediated immune escape,

and provide theoretical basis and clinical reference for solid tumor combined with immunotherapy.

2. Introduction to TAMs

The TME contains cancer cells, immune cells, cancer associated fibroblasts (CAFs), blood vessels and extracellular matrix (ECM), but immune regulation can simplify the focus on tumor associated macrophages (TAMs). The traditional m1/m2 dichotomy is too extensive. Single cell sequencing revealed that TAMs show a continuous lineage, with two core poles: CXCL9 + subpopulation (anti-tumor, activating CD8 + T) and SPP1 + subpopulation (pro tumor, immunosuppressive, pro fibrotic). The two phenotypes are plastic and can be converted to each other, and a single target to a subpopulation is easy to cause compensation. CAFs and ECM constitute the supporting skeleton, but the key to determine the clinical outcome is the cxcl9/spp1 ratio - high values predict the sensitivity of immunotherapy and good prognosis; Low values suggest drug resistance and short survival. TAMs mostly originate from circulating monocytes, and a small number of embryonic sources reside [1,2].

3. Introduction to SPP1⁺

3.1 Drug Resistance Mechanisms

SPP1 positive TAMs (SPP1 + TAMs) are prevalent in a variety of cancer species, and their sources are both bone marrow and peripheral tissue colonization lineages, suggesting that this subpopulation has highly conserved disease promoting functions in the TME. At the mechanism level, the complex network can be simplified into three intertwined main lines: first, SPP1 + TAMs and CAFs constitute a positive feedback loop - the former secretes SPP1 and tgf- β to drive fibroblasts to differentiate into a profibrotic phenotype, while the latter releases chemokines to maintain the pathogenic polarization of macrophages, jointly build an extracellular matrix barrier, and physically hinder T cell infiltration; Second, this subpopulation directly induces T cell exhaustion through soluble factors, recruits regulatory T cells and inhibits dendritic cell antigen presentation, and cooperates with myeloid derived suppressor cells and other inhibitory

macrophages to form a broad-spectrum immune rejection network; Third, SPP1 activates epithelial mesenchymal transition via CD44 and integrin pathways, and secretes chemokines and extracellular vesicles to remodel the distal microenvironment and pre condition tumor metastasis. The above pathways take the spp1-cd44 axis as the hub, couple matrix remodeling and metabolic competition, and jointly shape the immune checkpoint inhibitor tolerance ecosystem. In clinical transformation, a single intervention is easy to trigger compensation - clearing common anti-tumor macrophages highlights the advantage of SPP1 subpopulation, and blocking immune checkpoints or inhibiting CAFs alone activates bypass escape. Therefore, the multi-target joint strategy is more promising, and the core should simultaneously target SPP1 ligand receptor interaction, fibrotic matrix remodeling and key immune negative regulation pathways, so as to break up their coordinated defense.

3.2 Treatment Regimens and Combination Therapies

SPP1 targeted inhibitors include antibodies (such as 23c3/v1, kpl-404, and blocking peptides / aptamers) that directly neutralize SPP1 or block its binding to CD44, aiming to reverse cd8+t cell exhaustion; Small molecule inhibitors downregulate macrophage SPP1 from different links (nilotinib inhibits secretion, candi460 potently downregulates SPP1 in TAMs, shikonin indirectly reduces its expression, and csflr inhibitors (plx3397/plx5622) reduce release by depleting SPP1 + TAMs); Tetrahydrocurcumin, a natural active molecule, inhibits the pathway and blocks M2 polarization. Immune checkpoint inhibitors mainly include PD-1 MAb (pablizumab, navulizumab) and PD-L1 MAb (atilizumab, duvalizumab), which can restore T cell antitumor activity by blocking the pd-1/pd-l1 signaling axis. Antiangiogenic drugs (such as lenvatinib, sorafenib, regorafenib, and bevacizumab) inhibit VEGF secretion from spp1+tams and improve tumor hypoxia by targeting vegf/vegfr. Matrix targeted drugs include FAP inhibitors (sirolizumab, talabostat, Fapi ligand) to clear CAFs and disassemble the fibrotic barrier, and tgf- β pathway inhibitors (galunisertib, fresolimumab) to block matrix immunosuppression. Metabolic inhibitors from HIF-1 α / lactate (stiripentol, Nampt inhibitors YC-1), Adenosine

(oleclumab, ciforadenant) and tryptophan (epacadostat, indoximod) pathways block hypoxia induced polarization of spp1+ macrophages, adenosine immunosuppression and activation of treg/ myeloid suppression, respectively, and reverse metabolic immune escape.

The core combination strategy includes four categories: first, spp inhibitors combined with pd-1/pd-11 immune checkpoint inhibitors (ICIS) can reverse the depletion of cd8+t cells by blocking the spp1-cd44 pathway, relieve the immunosuppression of the PD-1 pathway, and double rebuild the antitumor function of cytotoxic T cells, which can effectively reduce drug-resistant tumors and remove distant pre metastatic micro foci in preclinical models of liver cancer, kidney cancer and colorectal cancer; Second, spp inhibitors combined with anti angiogenic drugs can not only inhibit the secretion of VEGF by SPP1 + macrophages and destroy the leaky immune barrier, but also alleviate the hypoxic microenvironment of tumors, reduce the infiltration of SPP1 + TAMs, and improve the penetration efficiency of immune cells and chemotherapy drugs into tumor tissues; The third is the triple therapy of tgf- β /fap matrix inhibitor, spp blocker and ICI, dismantling the spp1+tam-caf fibrotic immune barrier and solving the three core mechanisms of immune resistance, including physical barrier of extracellular matrix, T cell exhaustion and accumulation of multiple inhibitory immune cells, which has outstanding efficacy in pancreatic cancer and triple negative breast cancer models; Fourth, metabolic inhibitors combined with ICI can inhibit hypoxia / lactate mediated polarization of SPP1 macrophages, block the immunosuppressive loop brought by adenosine and tryptophan metabolism, and break the tumor immunosuppressive microenvironment.

The clinical optimal scheme is the triple combination of SPP targeting combined with immune checkpoint inhibitors + matrix / metabolic inhibitors, while relying on the spp1/cxcl9 ratio to screen drug-resistant population, so as to achieve precise reversal of immune resistance [3,4].

Ciforadenant (A2AR inhibitor) single agent can inhibit tumor and reduce spp1hi TAMs pre clinically in merpc; The combination of anti-PD-1 did not further reduce this group, but it synergized tumor shrinkage and prolonged survival by enhancing the infiltration of multifunctional CD8 $\square$ T cells. Mechanistically, spp1hi

TAMs escape clearance due to low csf1r, inhibit CD8 g T cells through hypoxia-cd73-adenosine-a2ar axis, and cause ICI primary resistance. A2AR blockade can relieve the inhibition and cooperate with pd- (L) 1. Limitations: only analyzing the adenosine /il-1r pathway, small samples, differences in different A2AR inhibitor regimens, and progress in animal models suggest multiple immune barriers. In phase I (nct02655822), ciforadenant combined with atezolizumab (n = 24) was well tolerated, PSA decreased $\geq 30\%$ in 25% of patients, some lesions regressed, and no objective remission was observed with single agent (n = 11); Future research needs to target SPP1 or CD73, spp1hi TAMs stratification, triple scheme, and verify in solid tumors [5].

3.3 SPP1 + Summary

In conclusion, SPP1 axis synergizes to drive ICI primary resistance through CD8 + T depletion, hypoxia adenosine A2AR pathway and fibrotic barrier. The triple strategy of targeting SPP1 combined with pd- (L) 1 and A2AR antagonist / matrix regulator can relieve immunosuppression at multiple levels, reverse T cell dysfunction and improve the TME.

4. TREM2 + Introduction

4.1 Drug Resistance Mechanism

TREM2 + TAMs derived from circulating Ly6C + monocytes initiate intracellular signaling cascades through adaptor protein DAP12 coupled with Syk kinase, and their core regulation can be summarized into three main pathways. At the metabolic level, the phosphatidylinositol 3-kinase (PI3K) - protein kinase B (Akt) - mammalian target of rapamycin (mTOR) axis drives lipid uptake and oxidative phosphorylation, laying the material foundation for its M2 like polarization and metabolic adaptation; At the transcriptional level, nuclear factor kappa B (NF- κ B) and signal transducer and activator of transcription 1 (STAT1) showed an inhibitory bias, preferentially transcribed negative regulators such as transforming growth factor beta (TGF- β) and IL-10, and upregulated PD-L1, while inhibiting the expression of type I interferon and T cell chemokine; At the antigen presentation level, the mitogen activated protein

kinase (MAPK) pathway significantly downregulated major histocompatibility complex class II (MHC-II) and costimulatory molecules, weakening the effective recognition of T cells. In terms of functional outcome, on the one hand, this group of TAMs cooperates with CAFs through the spp1-cd44 axis to build a physical barrier and induce the terminal depletion of CD8 + T cells, making them desensitized to PD-1 blockade; On the other hand, it antagonizes natural killer (NK) cells with the help of IL-18BP, and relies on il4i1-ccl8 signal to expand Foxp3 + regulatory T cells (Tregs). The above pathways are intertwined, creating multiple immune barriers covering metabolic adaptation, signal bias and physical exclusion in the microenvironment, and ultimately driving the occurrence of resistance to immune checkpoint inhibitor therapy.

4.2 Treatment Plan and Combination Therapy

At present, anti-tumor drugs targeting TREM2 are mainly divided into anti-trem2 monoclonal antibodies and small molecule inhibitors, and the anti-tumor effects of single drugs are limited. The anti-trem2 mAb includes mab178 without FC effect, afucosylated potent ADCC type mAb and pd-1-trem2 bispecific scFv. The former two remodel the TME by blocking ligand binding and scavenging TREM2 positive myeloid cells, respectively. The dual antibody can simultaneously target inhibitory myeloid cells and exhausted T cells, and modify CEA to target car-t secretion. The dual antibody can also achieve long-term tumor inhibition of colorectal cancer. However, the humanized monoclonal antibody py314, which entered phase I clinical practice, failed to achieve the expected efficacy and terminated development due to the problems of not screening the population with high TREM2 expression and the compensatory immunosuppressive pathway in advanced patients. Small molecule inhibitors include platinum artesunate conjugate OPA, artesunate, and HDAC inhibitor vorinostat/romidepsin, which directly target TREM2. These small molecules can downregulate TREM2 expression, promote the transformation of macrophagy to an antitumor phenotype, and reduce senescent immunosuppressive neutrophils. Sulfavant a, as a TREM2 agonist, has been controversial for its bi-directional regulation of promot-

ing T cell proliferation and upregulating Treg.

A large number of preclinical models have confirmed that the antitumor effect of various TREM2 targeted agents alone is weak. If they are combined with ICIS such as anti-PD-1/PD-L1, they can clear or reprogram TREM2 positive immunosuppressive myeloid cells, relieve the functional inhibition of CD8 + T and NK cells, enhance the infiltration of effector lymphocytes in the tumor, effectively overcome the resistance of immune checkpoint inhibitors, and produce a lasting antitumor effect [6,7].

Mite-144 is a TME-specific activating immune cytokine prodrug designed based on a three-tier structure. It mediates the enrichment of TREM2 + macrophages (TAMs) in tumors through the anti-trem2 targeting end. It relies on MMP14 to shear the linker peptide to release active IL-2 in tumors.

At the same time, the IL-2R β binding domain in the circulation blocks IL-2 Activity to reduce systemic toxicity. In the MC38 model, the single agent almost completely regressed the tumor, combined with anti-CTLA-4 completely cleared the tumor in 6 / 7 mice, and enhanced the killing function of CD8 + T cells and NK cells in human tumor tissues. Mechanistically, the drug can reverse the immunosuppression of TAMs by blocking TREM2, preferentially expand effector lymphocytes and mild Treg activation by local IL-2 pathway, and up regulate DC antigen presentation to jointly remodel the microenvironment; The safety is significantly better than that of traditional IL-2 and anti-trem2 mAb, which shows no systemic inflammation, liver and spleen toxicity and weight loss, and the tissue distribution is highly concentrated in tumors. This shear masking immune cytokine provides a general platform for myeloid targeted immunotherapy, but clinical transformation still needs more drug resistance models, large animal toxicology and deep macrophage phenotype mechanism research support [8].

4.3 TREM2 + Summary

In conclusion, trem2+ TAMs build an immunosuppressive barrier and drive ICIS resistance through PI3K Akt mTOR metabolic reprogramming, nf- κ b/stat1 transcriptional biased repression, and MHC-II downregulation. The effect of anti-trem2 mAb and small molecule alone is limited, and combined with pd-1/pd-l1 can re-

lieve the inhibition. The novel prodrug mite-144 targets TREM2, and the intratumoral MMP14 shear releases IL-2, reverses the inhibition, and achieves complete clearance in combination with anti-CTLA-4, which is safer than traditional therapy.

5. Introduction to CAF

5.1 Mechanism of Action

In solid tumors, iCAFs, myCAFs, and TAMs form a multilayered immunosuppressive network that contributes to primary resistance to immunotherapy. iCAFs produce inflammatory cytokines and chemokines and secrete complement components, thereby playing important roles in monocyte recruitment, inflammatory responses, complement activation, and the induction of immunosuppressive myeloid cell functions. In contrast, myCAFs participate in ECM remodeling, wound healing, and endothelial-to-mesenchymal transition, while secreting TGF- β . These factors can promote the M2-like polarization of immunosuppressive TAMs and regulate their lipid metabolism.

During the recruitment phase, CAFs secrete a variety of factors that regulate the recruitment and activation of myeloid cells. FAP⁺ CAFs secrete CCL2 to recruit circulating monocytes through the CCL2–CCR2 axis. iCAFs can further recruit monocytes through the CXCL12–CXCR4 and C3/C5 complement pathways and promote an immunosuppressive microenvironment, thereby facilitating monocyte infiltration into tumors. For example, TREM2⁺ TAMs secrete TGF- β 1, which activates fibroblasts and promotes collagen and ECM deposition, resulting in the formation of a dense stromal barrier that restricts the penetration of therapeutic antibodies and effector immune cells into the tumor.

5.2 Treatment Plan

AFS secreted CSF1 and APOE to further upregulate the expression of macrophagy TREM2, and continued to expand and inhibit myeloid cells; In the polarization phase, CAFs reprogram monocytes to induce tumor-promoting, immunosuppressive TAMs. Blocking the CAF-TAM interaction pathway, combined with immune checkpoint inhibitors, can effectively break the

matrix mediated immunosuppressive microenvironment, which is the current treatment idea [7,9].

6. Introduction to Lactic Acid

6.1 Mechanism of Action

Vahl effect-driven lactate accumulation can synergistically shape the M2-like tumor-promoting phenotype of TAMs through a multi-layer mechanism. This process can be simplified into three core hubs: microenvironment acidification, intracellular transcriptional reprogramming, and mitochondrial metabolism. At the microenvironment level, the decrease in extracellular pH (about 6.7-6.8) can directly upregulate M2 markers and weaken the inflammatory response. At the same time, lactate molecules, as signal ligands, initiate downstream tumor promoting transcriptional events after sensing by G protein coupled receptors; At the intracellular level, after lactate flows into macrophages via monocarboxylate transporters (mainly MCT1), on the one hand, it stabilizes hypoxia inducible factors to activate arginase and pro angiogenic factors, while inhibiting the pro-inflammatory signal of nuclear factor kappa B and upregulating immune checkpoint molecules, on the other hand, it is converted to pyruvate and relies on mitochondrial pyruvate carriers to enter the tricarboxylic acid cycle, providing the necessary energy and material basis for M2 polarization and immunosuppressive function by replenishing metabolic intermediates. It is worth noting that lactate efflux by tumor cells depends on MCT4, while uptake by immune cells depends on MCT1. The functional compensation of the two makes it difficult for a single target to work. Only blocking these transporters at the same time can effectively cut off the lactate shuttle cycle between tumor and immune cells. Finally, the four pathways of acidic environment, receptor sensing, metabolic adaptation and transcriptional regulation are intertwined, which jointly build a positive tumor promoting feedback loop with pH dependence and metabolic dependence. Targeting pH neutralization or mpc1 metabolic nodes in this loop is expected to become an effective strategy to reverse the immunosuppressive microenvironment.

Lactate also constitutes a metabolic epigenetic regulatory hub through the acetylation of histone and

non histone proteins, driving macrophages to polarize towards M2-like TAMs. At the histone level, after lactate flows through MCT1, h3k18la is catalyzed by p300/gcn5, which selectively activates M2 homeostasis/repair genes such as arg1 and IL-10, while inhibiting RARG transcription and activating STAT3 pathway to build an immunosuppressive microenvironment; At the non histone level, modifications such as pkm2 k62la and MeCP2 k271la synergistically promote M1 → M2 transition, while mre11/xrcc1 lactation enhances DNA repair and mediates chemoradiotherapy resistance, while aars1 mediated p53 lactation weakens its tumor suppressor function. Metabolically, lactate induced macrophages to turn to oxidative phosphorylation, and blocked their autophagic degradation through setdb1 mediated methylation of MCT1, forming a positive feedback loop of "lactate uptake → lactation → M2 polarization → more lactate transport"; At the same time, lactation and acetylation compete for histone lysine sites, crowding out acetylation during glycolysis enrichment to inhibit M1 pro-inflammatory genes, and acss2 generates lactyl CoA or acetyl CoA according to lactate concentration to guide the apparent program switching.

6.2 Treatment Plan

According to the above mechanisms, tumor treatment strategies targeting lactate metabolism and lactation can be systematically summarized as the following three directions: cutting off lactate production / transport, reversing lactation driven immunosuppression / drug resistance, and achieving synergy through combination therapy. At the metabolic level, it can target key enzymes of glycolysis (hK2 inhibitor 3-bromopyruvate, ldhA inhibitor fx11/gne-140), lactate transporter (MCT1 inhibitor azd3965 has entered phase I, MCT4 inhibitor vb124, dual target inhibitor SYROSINGOPINE), glucose uptake (GLUT1 inhibitor wzb117) and PDK (DCA clinical phase i/ii) to reduce lactate accumulation, alleviate acidification, reprogram TAMs from m2 to M1 polarization, and restore CD8 + T infiltration. At the level of lactation modification, by blocking cbp/p300/aars1 and other writing enzymes, inhibiting the lactation of DNA repair protein (mre11/xrcc1) to sensitize PARP inhibitors, or inhibiting aldh1a3 to reverse the chemoradiotherapy resistance of glioma, and even restoring the tumor suppressive function of p53 with β - alanine.

Combination therapy is the key to success or failure: lactate intervention combined with immune checkpoint inhibitors, car-t or chemotherapy (oxaliplatin) can break the ICIS resistance mediated by M2 TAMs, and enhance effector immune cell infiltration through ifn- γ -cxcl9/10 positive feedback loop, forming a benign cycle of "metabolic reprogramming immune activation"[10,11].

7. Conclusion

This paper systematically reviews the immunosuppressive network in TME with macrophages as the core and CAFs and metabolites as the support and its treatment strategies. The study found that SPP1 + and TREM2 + TAMs cooperatively build a physical barrier, induce CD8 + T cell exhaustion and recruit Treg cells through multi-level mechanisms such as spp1-cd44 axis, hypoxia adenosine A2AR pathway, tgf- β signaling and lactate metabolism, and jointly drive the primary drug resistance of immune checkpoint inhibitors. The efficacy of single target intervention is limited due to the rapid activation of compensatory pathways, and only the combined strategy can effectively break down multiple defenses: the triple scheme of SPP1 targeting combined with pd- (L) 1 and A2AR antagonist / matrix regulator, and the strategy of TREM2 targeting prodrug mite-144 combined with anti-CTLA-4, have shown significant advantages in reversing drug resistance and lasting tumor shrinkage in pre clinical models. Spp1/cxcl9 ratio was used to screen the beneficiaries, which provided an operable biomarker framework for precision medicine.

Current research remains largely limited to preclinical models and small early-phase trials, with insufficient evidence comparing different combination regimens and addressing TAM plasticity and treatment-related toxicity. Future studies should validate predictive biomarkers such as the SPP1/CXCL9 ratio and use single-cell multi-omics to optimize multi-target therapies in stromal-rich tumors.

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