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Research Progress on the Efficacy of PD-1 Inhibitors Combined with Chemotherapy in Advanced Gastric Cancer and the Regulatory Mechanism of Th1/Th2 Immune Balance

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Abstract: Advanced gastric cancer is highly malignant, and traditional chemotherapy has limited efficacy. Currently, combining PD-1 inhibitors with chemotherapy represents a significant breakthrough in immunotherapy for this disease. This article reviews clinical evidence on the efficacy of PD-1 inhibitors combined with chemotherapy in advanced gastric cancer and the regulatory mechanism of Th1/Th2 immune balance. It explores the advantages of the combination strategy in terms of objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). The combination therapy can harness cytotoxic effects to release tumor antigens, actively reshape the tumor immune microenvironment, and regulate key molecules such as MFSD2A. However, the predictive value of biomarkers is limited, and strategies to reverse the Th2-dominant microenvironment are immature, necessitating the integration of multi-omics data to construct precise predictive models. Future efforts should focus on developing novel combination regimens, establishing a multidimensional biomarker system, and optimizing individualized immune regulatory strategies to further enhance long-term survival benefits for patients with advanced gastric cancer.

Keywords: Advanced gastric cancer; PD-1 inhibitors; Combined chemotherapy; Th1/Th2 immune balance; Immune microenvironment

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1. Introduction and research value positioning

1.1. Clinical challenges and immunotherapy needs in advanced gastric cancer

Advanced gastric cancer (AGC) is characterized by high heterogeneity, concealed early symptoms, and frequent distant metastasis at diagnosis, resulting in a poor prognosis with a 5-year survival rate of less than 30%. Traditional chemotherapy regimens based on platinum and fluorouracil can provide some relief

but have limited ORR and are prone to drug resistance and disease progression [1]. In recent years, with a deeper understanding of the tumor immune microenvironment, immune checkpoint inhibitors, particularly programmed death receptor-1 (PD-1) inhibitors, have been approved for second-line treatment of advanced gastric cancer and have demonstrated significant potential for survival benefits in multiple clinical trials [2]. For example, the KEYNOTE-859 Phase III clinical trial confirmed that pembrolizumab combined with chemotherapy significantly improved OS (HR = 0.78, $p < 0.0001$) in previously untreated patients with locally advanced or metastatic HER2-negative gastric cancer, with manageable safety, suggesting that this combination strategy has the potential to become a first-line standard treatment [3]. These advances highlight the urgent clinical need for immunotherapy in advanced gastric cancer, especially in overcoming the limitations of traditional chemotherapy, prolonging survival, and improving quality of life.

1.2. The central role of the PD-1/PD-L1 pathway in tumor immune escape

The PD-1/PD-L1 signaling pathway is one of the key mechanisms by which tumors achieve immune escape. Tumor cells evade immune surveillance by overexpressing PD-L1, which binds to PD-1 on the surface of T cells, inhibiting T cell activation, proliferation, and cytotoxic function. Abnormal activation of this pathway is particularly prominent in gastric cancer. Studies have found that the IKZF4/NONO-RAB11FIP3 axis can enhance membrane surface expression of PD-L1 by promoting its endosomal recycling, thereby strengthening immunosuppressive effects; inhibiting RAB11FIP3 or IKZF4 can significantly promote CD8+ T cell infiltration and enhance their cytotoxicity, effectively inhibiting tumor progression [4]. Notably, although PD-1 monoclonal antibodies have shown significant efficacy in some patients, not all patients with high PD-L1 expression benefit, indicating that the functional regulation of this pathway is far more complex than simple protein expression and involves multiple mechanisms such as endocytic recycling, gene polymorphisms, and microenvironment interactions. Therefore, in-depth analysis of the dynamic regulatory network of the PD-1/PD-L1 pathway in gastric cancer immune escape is crucial for optimizing immunotherapy strategies.

1.3. The association between Th1/Th2 immune balance and antitumor efficacy

The polarization state of helper T cell (Th) subsets, particularly the balance between Th1 and Th2, is a core factor determining the efficacy of antitumor immune responses. Th1-type immune responses, characterized by the secretion of pro-inflammatory cytokines such as IFN-γ and TNF-α, can activate CD8+ T cells and macrophages, exerting potent antitumor effects; whereas Th2-type responses, dominated by IL-4 and IL-10, tend to induce immune tolerance and promote tumor progression. For example, in patients with advanced gastroesophageal adenocarcinoma, pembrolizumab combined with chemotherapy can induce the formation of an “immune hub” in the tumor microenvironment containing CXCL13+ tumor-reactive T cells and interferon-stimulated gene programs, significantly increasing CD8+ T cell infiltration, suggesting the establishment of a Th1-dominant state [5]. Similarly, neoadjuvant chemotherapy alone can also reduce the proportion of FOXP3+ Tregs, increase CD8+ T cell levels, and be accompanied by increased TCR diversity, indicating that chemotherapy itself has the ability to reshape the Th1/Th2 balance [6].

2. Clinical efficacy evaluation of PD-1 inhibitors combined with chemotherapy

2.1. Clinical evidence of objective response rate and survival benefits

In recent years, multiple high-quality clinical studies have confirmed that PD-1 inhibitors combined with

chemotherapy can significantly improve ORR and prolong patient survival in advanced gastric cancer treatment. In the CheckMate 649 study, nivolumab combined with chemotherapy significantly improved OS and PFS in patients with a PD-L1 combined positive score (CPS) ≥5, establishing this regimen as a first-line standard treatment [7]. In a randomized, double-blind, placebo-controlled Phase III clinical trial conducted in China (NCT03745170), cemiplimab combined with XELOX chemotherapy significantly improved median OS in patients with unresectable locally advanced or metastatic gastric/gastroesophageal junction cancer (overall population: 15.2 months vs 12.3 months, HR 0.77; PD-L1 CPS ≥ 5 subgroup: 18.4 months vs 12.9 months, HR 0.66) [8]. In patients with HER2-negative unresectable advanced or metastatic gastric cancer, a Phase 1b/2 study showed that cadonilimab combined with chemotherapy achieved an ORR of 52.1% (95% CI 41.6–62.5) and a median OS of 17.48 months (95% CI 12.35–26.55), with even higher values of 20.32 months in patients with PD-L1 CPS ≥ 5 [9]. For HER2-positive patients, the KEYNOTE-811 study confirmed that adding pembrolizumab to trastuzumab combined with chemotherapy significantly improved ORR and induced partial complete responses [10]. These data collectively indicate that PD-1 inhibitors combined with chemotherapy not only enhance tumor regression but also translate into statistically and clinically significant survival advantages.

2.2. Comparative efficacy studies with traditional chemotherapy regimens

In the Chinese population, the cemiplimab combined with XELOX regimen also demonstrated superior OS benefits compared to placebo combined with chemotherapy. Notably, even in the overall population without biomarker screening, PD-1 inhibitors combined with chemotherapy can still provide survival benefits. For example, global multicenter observational data and clinical practice guidelines indicate that for patients with advanced gastric cancer expressing PD-L1, combination therapy can prolong survival by approximately 3 months compared to chemotherapy alone [11]. In addition, anti-PD-1 combined with chemotherapy has been recommended as a first-line treatment option for unselected advanced gastric/gastroesophageal junction adenocarcinoma, reflecting its broad applicability and superiority over traditional chemotherapy [12]. However, not all combination regimens involving immune checkpoint inhibitors can surpass chemotherapy alone. For example, in the PRODIGE 59-FFCD 1707-DURIGAST study, FOLFIRI combined with durvalumab (a PD-L1 inhibitor) or further combined with tremelimumab (a CTLA-4 inhibitor) was used in patients who progressed after platinum-based chemotherapy. Although some PFS advantages were observed in the PD-L1 TPS ≥ 1% subgroup, the overall study did not meet the primary endpoint, suggesting that simply adding immunotherapy in second-line or later treatment may not replicate the benefits of first-line combination therapy [13]. This highlights the critical impact of treatment line, patient selection, and drug combination on efficacy.

2.3. Efficacy differences among different combination regimens (e.g., DCF regimen)

Currently, research data on the efficacy differences between PD-1 inhibitors combined with different chemotherapy backbones (such as FLOT, SOX, XELOX, DCF, etc.) are insufficient, but preliminary explorations have been conducted. A Phase II study (NEOSUMMIT-01) using toripalimab combined with oxaliplatin-based perioperative chemotherapy significantly improved the TRG 0/1 rate (44.4% vs 20.4%, $P = 0.009$) [14].

In China, the SOX regimen (S-1 combined with oxaliplatin) as perioperative chemotherapy has been shown to be non-inferior to FOLFOX (3-year OS rate 75.2% vs 67.8%) [15], suggesting that oxaliplatin-

containing regimens are well tolerated and effective in the Asian population and may provide an ideal backbone for PD-1 inhibitor combinations. In addition, neoadjuvant/conversion therapy with camrelizumab combined with apatinib and S-1±oxaliplatin achieved a pCR rate of 15.8% in locally advanced gastric cancer with cT4a/bN+, and efficacy was associated with microsatellite instability (MSI), PD-L1 expression, and tumor mutation burden [16].

Although DCF (docetaxel + cisplatin + 5-FU) is an effective chemotherapy regimen for advanced gastric cancer, no large-scale studies have specifically evaluated the efficacy of PD-1 inhibitors combined with DCF in gastric cancer. Current evidence mostly focuses on FLOT, XELOX, or oxaliplatin/fluorouracil-containing regimens. Notably, in the KEYNOTE-585 study, pembrolizumab combined with platinum-based doublet chemotherapy (usually 5-FU + cisplatin or capecitabine + oxaliplatin) significantly improved the pCR rate (12.9% vs 2.0%, $P < 0.00001$) and prolonged event-free survival in neoadjuvant/adjuvant treatment [17]. This suggests that platinum-based doublet chemotherapy backbones have synergistic potential when combined with PD-1 inhibitors, but the choice of specific regimens needs to consider efficacy, toxicity, and regional medication habits.

In summary, PD-1 inhibitors combined with different chemotherapy regimens have shown superior clinical benefits compared to chemotherapy alone, with the most substantial evidence supporting regimens based on platinum-based doublets (such as XELOX and FLOT). Future head-to-head comparative studies are needed to identify the optimal chemotherapy backbone further to achieve a balance between maximizing efficacy and minimizing toxicity.

3. Regulatory mechanisms of Th1/Th2 immune balance

3.1. Differentiation and functional characteristics of Th1/Th2 cells

Helper T cells (Th) can be divided into two major subsets, Th1 and Th2, based on their cytokine profiles and functions. These subsets play distinct roles in anti-tumor immunity. Th1 cells primarily secrete interferon-gamma (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor-beta (TNF-β), promoting cellular immune responses and activating macrophages and cytotoxic $CD8^+$ T cells, thereby enhancing the clearance of tumor cells. Conversely, Th2 cells predominantly produce cytokines such as IL-4, IL-5, IL-6, and IL-10, which tend to induce humoral immune responses and, in certain contexts, suppress Th1-mediated anti-tumor effects, even promoting tumor immune evasion [18]. In the tumor microenvironment, shifts in the Th1/Th2 balance directly influence the efficacy of immunotherapy: a Th1-dominant state is generally associated with favorable anti-tumor responses, whereas a Th2-dominant state often correlates with immune suppression and disease progression. For instance, in patients with advanced gastric cancer, elevated levels of Th2-type cytokines such as IL-4, IL-6, and IL-10 are associated with small intestinal injury and activation of inflammatory pathways, suggesting that Th2 polarization may exacerbate immune imbalance [21].

3.2. Impact of PD-1 signaling on Th1/Th2 polarization

The PD-1/PD-L1 signaling pathway not only directly inhibits T cell activation but may also influence the Th1/Th2 immune balance by regulating Th cell polarization. Although existing literature does not explicitly describe the direct regulatory mechanisms of PD-1 signaling on Th1/Th2 differentiation, multiple indirect lines of evidence support its crucial role in this process. For example, in untreated patients with metastatic melanoma, baseline levels of Th1 cytokines (e.g., IFN-γ) are significantly lower than those in healthy

controls, whereas responders to PD-1 inhibitor therapy exhibit a marked increase in IFN-γ levels by week 6, suggesting that PD-1 blockade promotes Th1 polarization [19]. In advanced gastric cancer, the IKZF4/NONO-RAB11FIP3 axis mediates immune evasion by enhancing PD-L1 membrane expression, while inhibiting this axis increases $CD8^+$ T cell infiltration and promotes T cell proliferation, indirectly supporting the restoration of Th1-type immune responses. Notably, in the gastric cancer microenvironment, lactate accumulation can upregulate PD-1 expression on regulatory T cells (Tregs), causing PD-1 inhibitors to preferentially activate immunosuppressive Tregs rather than effector T cells, potentially weakening Th1 responses [20]. This suggests that the impact of PD-1 signaling on the Th1/Th2 balance is highly dependent on the metabolic state of the microenvironment.

3.3. Dynamic changes in key cytokines (IFN-γ, IL-4, etc.)

IFN-γ and IL-4, as core effector molecules of Th1 and Th2 responses, respectively, serve as important indicators for assessing the Th1/Th2 balance during immunotherapy. In the context of PD-1 inhibitor therapy, elevated IFN-γlevels typically correlate positively with treatment response. Various intervention strategies can enhance IFN-γproduction: for example, FX-11@PEG-Ce6 promotes $CD8^+$T cell secretion of IFN-γby alleviating tumor microenvironment acidity, synergistically enhancing anti-PD-1 efficacy [21]; high expression of MFSD2A reduces T cell exhaustion by inhibiting the COX2-prostaglandin-TGFβ1 axis, thereby improving IFN-γ secretion capacity [22]. Conversely, elevated levels of Th2-type cytokines such as IL-4 are often associated with poor prognosis. The REGOMUNE study found that in patients with advanced gastric cancer who did not respond to regorafenib combined with avelumab, peripheral blood IL-4 levels were significantly elevated, accompanied by increased infiltration of M2 macrophages, suggesting that a Th2-type inflammatory environment may drive immunotherapy resistance [23]. Therefore, monitoring the dynamic changes in cytokines such as IFN-γ and IL-4 not only helps assess the Th1/Th2 balance but also serves as a potential biomarker for predicting the efficacy of PD-1 inhibitors combined with chemotherapy.

4. PD-1/PD-L1 pathway and immune microenvironment remodeling

Tumor-associated macrophages (TAMs), as a major component of the tumor microenvironment (TME), not only participate in establishing an immunosuppressive state but also play a key role in regulating the efficacy of PD-1/PD-L1 inhibitors [24]. Multiple studies have shown that TAMs can highly express PD-L1 and inhibit T cell function by binding to PD-1 on the surface of T cells. In breast cancer patients, single-cell transcriptomic and spatial multiplex immunofluorescence analyses reveal that PD-L1+ TAMs exhibit mature and immunostimulatory characteristics and are spatially proximal to CD8+ T cells; higher density or proportion of these cells correlates with better clinical prognosis. Notably, PD-L1 expression can spontaneously upregulate during monocyte-to-macrophage differentiation without exogenous IFN-γstimulation and can promote CD8+ T cell proliferation and cytotoxic function [25]. Additionally, in esophageal squamous cell carcinoma (ESCC), $PD\text{-}L1^+$TAMs also correlate positively with clinical benefit, and in vitro PD-L1 blockade induces TAM reprogramming toward a pro-inflammatory phenotype [26]. However, TAMs exhibit highly heterogeneous functions. For example, in cholangiocarcinoma, PD-L1 is primarily expressed by M2-type TAMs, mediating CD8+ T cell exhaustion and forming an immunosuppressive microenvironment; in contrast, the density of non-exhausted PD-1+EOMES+CD8+ effector T cells correlates significantly with longer survival [27]. Further

research has found that targeting TAMs can enhance the efficacy of PD-1/PD-L1 blockade. For instance, in the Mycn-nGEMM neuroblastoma mouse model, although tumor cell PD-L1 expression is low, macrophages highly express PD-L1, and anti-PD-L1 therapy effectively depletes anti-inflammatory macrophages and increases T cell infiltration; combining this with a CD40 agonist antibody further improves survival rates [28]. Similarly, PI3Kγ inhibitors combined with anti-PD-1/PD-L1 therapy can reprogram TAMs by regulating the PI3Kγ-AKT-NF-κB pathway, reducing myeloid-derived suppressor cells, increasing CD8+ T cell numbers and pro-inflammatory cytokine levels, thereby reversing the immunosuppressive microenvironment [29]. However, strategies targeting TAMs also face challenges. A phase I clinical study showed that although the CSF-1R inhibitor pexidartinib reduces CD14+CD16+ monocytes in peripheral blood, it also impairs dendritic cell differentiation and function, potentially limiting its anti-tumor activity [30]. These findings suggest that TAMs play a dual role in PD-1/PD-L1 pathway-mediated immune microenvironment remodeling, and their regulation requires balancing pro-inflammatory and immunostimulatory functions.

5. Current controversies and challenges in research

5.1. Limitations of biomarker predictive efficacy

Although PD-1 inhibitors combined with chemotherapy have demonstrated clinical benefits in treating advanced gastric cancer, existing biomarkers exhibit significant limitations in predicting efficacy. Commonly used predictive indicators such as PD-L1 combined positive score (CPS), microsatellite instability (MSI) status, and tumor mutation burden (TMB) show poor predictive consistency across different patient populations [31]. However, not all patients with high TMEscore achieve ideal outcomes, indicating that single-dimensional biomarkers cannot fully capture the complexity of the tumor immune microenvironment. Additionally, although high expression of HSPA4 correlates with a favorable response to chemotherapy combined with anti-PD-1 therapy, it predicts poor prognosis in patients undergoing surgery alone, reflecting contradictory predictive values of this marker across different treatment contexts [32]. Similarly, although lymphoid radiomic scores (LRS) and myeloid radiomic scores (MRS) constructed based on CT imaging can assess immune microenvironment status, objective response rates vary significantly among patients with different imaging subtypes (type 1: 27.3%, type 2: 53.3%, type 3: 10.2%, type 4: 30.0%), further highlighting the heterogeneity and uncertainty of current predictive models [33]. Although multidimensional tumor-infiltrating immune cell (TIIC) signatures constructed via multiplex immunohistochemistry aid in predicting responses to anti-PD-1/PD-L1 therapy, their clinical adoption remains limited by issues of technical standardization and reproducibility [34]. Therefore, there is an urgent need to integrate multi-omics data to construct more robust and universally applicable predictive systems.

5.2. Regulatory challenges in Th2-dominant microenvironment formation

A Th2-type immune-dominant microenvironment is considered one of the key factors limiting the efficacy of PD-1 inhibitors, but its formation mechanisms and intervention strategies remain challenging. Although high expression of MFSD2A can reduce TGFβ1 release by inhibiting COX2-prostaglandin synthesis, thereby enhancing CD8+ T cell activation and improving Th1/Th2 imbalance, the clinical targetability of this pathway remains to be validated. On the other hand, PRDM15 may indirectly promote Th2 polarization by activating the PVR/TIGIT axis to inhibit T cell function, but its specific regulatory role in Th1/Th2 balance remains unclear [35]. Therefore, effectively reversing or preventing the formation of a Th2-dominant

microenvironment remains a core challenge in optimizing current combination therapy strategies.

6. Future research directions

6.1. Exploration of novel combination therapy strategies

Although current PD-1 inhibitors combined with chemotherapy have shown significant clinical benefits in treating advanced gastric cancer, a substantial proportion of patients still do not benefit or develop resistance. Therefore, exploring novel combination therapy strategies with stronger synergistic effects is an important future research direction. In recent years, multi-mechanism interventions targeting immunosuppressive pathways have gradually gained attention. For example, inhibiting RAB11FIP3 or IKZF4 can block PD-L1 endosomal recycling, enhancing T cell infiltration and cytotoxicity, suggesting that this axis may serve as a novel target for gastric cancer immunotherapy. Additionally, PRDM15 inhibits T cell function by activating the PVR/TIGIT axis, providing a theoretical basis for combining TIGIT inhibitors [36]. The development of nanomedicine platforms also offers new ideas for combination therapy. For instance, the FX-11@PEG-Ce6 nanosystem promotes dendritic cell maturation and enhances CD8+ T cell function by alleviating acidic microenvironments, thereby improving PD-1 inhibitor efficacy; another class of mesoporous polydopamine-based nanoparticles loaded with oxaliplatin and manganese dioxide, combined with mild photothermal therapy, can induce immunogenic cell death, activate the cGAS-STING pathway, and significantly enhance anti-tumor immune responses. Furthermore, fecal microbiota transplantation (FMT) combined with PD-1 inhibitors has shown preliminary efficacy in previously resistant patients, with an objective response rate of 20%, suggesting that modulating the gut microbiota may represent a novel strategy for overcoming immunotherapy resistance [37]. These cutting-edge explorations lay the foundation for constructing multidimensional, multi-layered combination therapy systems.

6.2. Construction of multi-omics biomarker systems

Although PD-L1 expression (e.g., CPS score) has been used to guide PD-1 inhibitor therapy, its predictive efficacy remains limited, necessitating the integration of multi-omics data to construct more precise biomarker systems. Studies have shown that high expression of MFSD2A correlates with a favorable response to anti-PD-1 therapy, with mechanisms involving inhibition of COX2-prostaglandin synthesis, reduced TGFβ1 release, and enhanced CD8+ T cell activation, suggesting that MFSD2A may serve as a potential predictive marker [38]. Although high expression of HSPA4 correlates with poor prognosis in patients undergoing surgery alone, it correlates with a better treatment response in those receiving PD-1 inhibitors combined with chemotherapy, further highlighting the dynamic nature of biomarkers in the context of combination therapy [39]. Additionally, PD-L1 gene polymorphisms (e.g., the P146R mutation caused by rs17718883) can weaken PD-1/PD-L1 interactions, enhance IFN-γ secretion, and inhibit tumor growth, but patients with this mutant type do not derive additional benefits from PD-1 monoclonal antibodies, suggesting that this polymorphism may be used to exclude ineffective treatments [40]. Immune microenvironment classification systems (e.g., TIME-inflamed, TIME-desert, TIME-excluded) also exhibit predictive value, with patients in the TIME-inflamed subtype more likely to benefit from pembrolizumab combined with chemotherapy [41]. Future research should integrate multi-dimensional data from genomics, transcriptomics, proteomics, and immune cell atlases, combined with artificial intelligence algorithms, to establish dynamic, quantifiable comprehensive predictive models for precise stratification and individualized treatment decision-making.

6.3. Optimization of individualized immune regulation strategies

The core of individualized immune regulation lies in customizing treatment plans based on patients' tumor immune microenvironment characteristics, host immune status, and molecular subtypes. Studies have shown that EBV-positive gastric cancer exhibits higher CD8+ T cell infiltration and interferon-induced gene expression, whereas EBV-negative gastric cancer highly expresses genes related to the COX-2/PGE2 pathway, suggesting that different molecular subtypes may respond differently to immunotherapy. The status of Helicobacter pylori infection may also influence the efficacy of PD-1 inhibitors, and although existing research conclusions remain controversial, its interactions with the gut microbiota and immune infiltration warrant further exploration. Additionally, single-cell sequencing reveals that after neoadjuvant PD-1 inhibitor therapy combined with chemotherapy, CD3+, CD8+ T cells, and NK cells significantly increase in the tumor microenvironment of patients with major pathological response (MPR), whereas regulatory T cells (FOXP3+) are predominantly enriched in non-MPR patients, indicating that dynamic changes in Treg cells can serve as efficacy monitoring indicators. Chemotherapy itself can also remodel the immune microenvironment, such as reducing FOXP3+ Treg proportions and increasing CD8+ T cell levels after neoadjuvant chemotherapy, accompanied by increased TCR diversity, providing a basis for optimizing the timing of combination therapy. Future strategies should be based on patients' baseline immune characteristics (e.g., Th1/Th2 cytokine profiles, T cell exhaustion status, myeloid cell composition) combined with dynamic immune monitoring during treatment (e.g., changes in peripheral blood cytokines) to optimize dosing schedules, doses, and drug combinations, achieving a transition from a "one-size-fits-all" to a "tailored" treatment model.

7. Summary and clinical translation significance

In recent years, significant progress has been made in understanding the core mechanisms of PD-1 inhibitors combined with chemotherapy for treating advanced gastric cancer. Multiple studies have demonstrated that this combination strategy not only enhances antigen release by directly killing tumor cells but also significantly remodels the tumor immune microenvironment, promoting Th1-type immune responses and suppressing Th2-dominant states. For example, neoadjuvant PD-1 inhibitor therapy combined with chemotherapy significantly increases CD3+, CD8+ T cell, and NK cell infiltration in the tumor microenvironment while reducing FOXP3+ regulatory T cell proportions, thereby improving the Th1/Th2 balance. Additionally, chemotherapy itself has been shown to increase TCR diversity and enhance CD8+ T cell activity, laying an immunological foundation for PD-1 inhibitor efficacy. At the molecular level, high expression of MFSD2A can enhance CD8+ T cell function and reduce exhaustion by inhibiting the COX2-prostaglandin pathway to decrease TGFβ1 release, improving anti-PD-1 treatment response; the IKZF4/NONO-RAB11FIP3 axis regulates T cell cytotoxicity by influencing PD-L1 membrane expression, highlighting its key role in Th1/Th2 polarization. These findings collectively reveal the synergistic mechanisms by which PD-1 inhibitors combined with chemotherapy modulate the immune microenvironment, reverse T cell exhaustion, and optimize the Th1/Th2 balance through multiple dimensions.

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