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Synergistic Antitumor Effects and Pharmacological Interactions of Immune Checkpoint Inhibitors Combined with Chemotherapeutic Agents: Mechanisms and Clinical Translation

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Abstract: This paper provides a comprehensive literature review of the combination of immune checkpoint inhibitors (ICIs) and chemotherapy drugs in the field of synergistic antitumor therapy, aiming to summarize and analyze the current status, key issues, and future trends of tumor chemotherapy combined with immunotherapy. Research indicates that chemotherapy drugs enhance the immune system's ability to recognize and kill tumors by inducing immunogenic cell death (ICD) and altering the tumor microenvironment (TME). This paper provides a detailed analysis of drug metabolism enzymes and transporters, time-dependent interactions, dual pathways for immune system activation, intrinsic sensitization of tumor cells, the microbiome-immunotherapy axis, mechanisms of resistance and reversal strategies, as well as breakthroughs in novel delivery systems. Finally, this paper discusses improvements and prospects for future immunotherapy-chemotherapy combination studies. Personalized dosing and toxicity management remain major challenges, and future efforts should focus on optimizing treatment regimens using multi-omics data and organoid/PDX models.

Keyword: Immune checkpoint inhibitors; immunochemotherapy; synergistic antitumor effects; tumor microenvironment; novel delivery systems

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1. Introduction

In recent years, the field of tumor immunology has made breakthrough progress. With in-depth research into immune checkpoint inhibitors and targeted drugs, immune combination therapy has demonstrated significant clinical efficacy improvements in the treatment of certain advanced or difficult-to-cure cancers using conventional therapies. For example, in the KEYNOTE-189 study, Marina C. Garassino's team confirmed through a phase III randomized controlled trial that for patients with metastatic squamous non-small cell lung cancer without EGFR/ALK mutations, pembrolizumab

combined with pemetrexed and chemotherapy significantly improved patient survival benefits, objective response rates, and prognosis[1]. Similarly, the IMpower150 study (Reck et al.) used a three-arm randomized controlled Phase III trial model to find that for patients with metastatic non-squamous non-small cell lung cancer who were treatment-naive to chemotherapy, the combination of atezolizumab with bevacizumab and carboplatin/paclitaxel (ABCP) regimen resulted in clinically meaningful survival benefits[2]. These important findings provide key evidence-based support for immune combination therapy in advanced or metastatic tumors, particularly for patients who are difficult to treat with targeted therapy, and suggest that this therapy may be particularly beneficial for specific populations.

2. Pharmacological Interactions

2.1. Drug metabolism enzymes and transporter-mediated interactions

2.1.1. Cytochrome P450 (CYP450) and the metabolism of chemotherapeutic drugs

The cytochrome P450 (CYP450) enzyme system is closely associated with the metabolism of chemotherapeutic drugs, and its activity exerts a dual regulatory effect on both the efficacy of the drugs and their toxic side effects on the body. Certain chemotherapy drugs, such as cyclophosphamide, lack drug activity in the body and must be converted into the active form, oxyacetylnitrosourea, through the action of CYP2B6 within the CYP450 family to exert their antitumor effects. Additionally, certain drugs undergo CYP450 metabolism, converting from lipophilic to hydrophilic substances, which are more easily excreted, reducing accumulation in the body and lowering the risk of toxicity from chemotherapy drugs. If the effect of CYP450 is too potent, it may accelerate the metabolism of chemotherapy drugs. For example, irinotecan undergoes enhanced metabolism under the action of CYP3A4, leading to reduced blood drug concentrations and weakened therapeutic efficacy[3]. Abnormal expression of CYP450 in tumor tissues may induce tumor resistance to chemotherapy drugs. Individual differences in the CYP450 enzyme system are regulated by genetic polymorphisms, patient physiological factors, disease status, and drug interactions. Therefore, when applying chemotherapy drugs clinically, it is necessary to comprehensively consider the patient's genotype, physical condition, and organ function. By detecting the activity of CYP450 in the body or adopting genomic strategies, the application of chemotherapy drugs can be optimized to reduce efficacy differences and adverse reaction risks in individualized treatment.

2.1.2. Regulatory role of ABC transporters

As members of the ATP-binding cassette (ABC) transmembrane transporter superfamily, ABC transporters mediate treatment resistance in the tumor immune microenvironment through a dual mechanism. First, ABC transporters utilize the energy generated by ATP hydrolysis to actively pump chemotherapy drugs out of cancer cells, resulting in insufficient drug concentrations inside the cells and preventing effective induction of tumor cell death and tumor antigen release. This hinders the adequate activation of antigen-presenting cells toward T cells, leading to T cell activation dysfunction. Second, drug-resistant cancer cells can alter the immunosuppressive characteristics of the tumor microenvironment (TME) through ABC transporter-mediated metabolite secretion, further inhibiting T cell infiltration and function. Ultimately, these mechanisms collectively weaken T cell recognition and killing of tumors, promoting the formation of an "immunocold" tumor phenotype. Specific transporters such as P-glycoprotein (P-gp/ABCB1) and multidrug resistance-associated protein 2 (MRP2/ABCC2) can specifically efflux platinum-based and anthracycline-based chemotherapy drugs. This efflux activity abnormally activates the PI3K/Akt signaling pathway, leading to phosphorylation of the GSK-3β Ser9 site downstream, which in turn upregulates the expression of ABC transporters, forming a positive feedback loop that reduces intracellular drug accumulation.

Clinical studies have confirmed that high expression of ABC transporters is significantly associated with poor prognosis in various malignant tumors, including colorectal cancer and lung cancer. Their expression is also regulated by immune-related factors such as heat shock proteins and cytokines. Although existing ABC transporter inhibitors can partially reverse multidrug resistance (MDR), their potential interference with the normal physiological functions

of immune cells requires careful evaluation, presenting a significant challenge for the development of precise targeted regulatory strategies.

2.2. Time-dependent interactions

In recent years, multiple studies have demonstrated that the efficacy of combination therapy involving chemotherapy and immunotherapy is closely related to the sequence of treatment administration. The core mechanism involves using neoadjuvant chemotherapy to reshape the tumor microenvironment, thereby synchronizing immune activation to precisely target tumor cells. Preliminary chemotherapy activates immunogenic cell death by inducing tumor cell death, releasing tumor antigens, and reshaping the TME. Subsequent immunotherapy can capture the neoantigens induced by chemotherapy, promoting T-cell clonal expansion and tumor cell infiltration, thereby forming a chemotherapy-immunotherapy synergistic effect. However, concurrent administration may inhibit T-cell activation or immune cell clearance, thereby weakening the immune response. Research by Zhang Yi et al. demonstrated that altering the timing of treatment through immunotherapy combined with chemotherapy in advanced NSCLC patients with negative driver genes[4] maximized ORR and PFS when immunotherapy was administered 3–5 days after chemotherapy, achieving "chemotherapy clearance-immunotherapy consolidation" spatiotemporal synergy, providing clinical evidence for precise sequential therapy and achieving sequential enhancement of antitumor effects.

This is related to the window period of chemotherapy-induced immunogenic cell death (ICD). Studies have shown that Obeid et al. found through the relationship between the surface exposure of the ICD marker CALR and the time after chemotherapy[5] that the peak period of ICD generally occurs 48-72 hours after chemotherapy. However, this period may be shortened or prolonged due to rapid repair mediated by RHOJ-represented EMT-related tumor cells or microenvironment regulation mediated by the CAF-MMP3 axis. Therefore, individualized markers such as RHOJ and MMP3 can be used to predict the window period, which is typically associated with CRT exposure and HMGB1 release. In clinical translation, PD-1/PD-L1 inhibitors are often combined with chemotherapy 48 hours post-treatment to enhance antigen presentation, while monitoring CAF activity to avoid immune suppression rebound[6].

3. Synergistic Mechanisms

3.1. Dual pathways of immune system activation

3.1.1. Activation of innate immunity

Traditional chemotherapy drugs can reshape the tumor microenvironment, creating conditions for the immune system to recognize and attack tumor cells. Specifically, chemotherapy drugs can induce immunogenic cell death (ICD) in tumor cells, releasing tumor antigens and damage-associated molecular patterns (DAMPs). These signaling molecules can effectively activate innate immune cells, such as dendritic cells (DCs), macrophages, and natural killer cells (NK cells).

Chemotherapy can significantly enhance the activity and killing capacity of NK cells. The mechanisms include inducing tumor cells to express higher levels of NK cell-activating ligands (such as MICA/B, ULBP, etc., which can be recognized by the NK cell receptor NKG2D), thereby promoting NK cell recognition and killing of tumors; and altering the tumor microenvironment (TME) to reduce its inhibitory effects on NK cells. For example, chemotherapy can reduce the number of myeloid-derived suppressor cells (MDSCs) and inhibit their function, thereby alleviating their suppression of NK cell activity[7]. Chemotherapy-induced tumor cell death and tissue damage trigger local inflammatory responses, releasing various chemokines (such as CCL5, CXCL10) and cytokines. These mediators effectively recruit innate immune cells to the tumor site, increasing local immune cell infiltration and thereby enhancing the killing of tumor cells.

3.1.2. Enhancement of adaptive immunity

3.2. Intrinsic sensitization of tumor cells

Immunotherapy combined with chemotherapy has emerged as a key strategy for enhancing antitumor immune responses by inducing intrinsic sensitization of tumor cells—primarily manifested through the synergistic effects of upregulation of MHC-I molecule expression and the release of tumor neoantigens. Taking oxaliplatin as an example, this drug triggers multiple immune activation signals by inducing immunogenic cell death (ICD):[8] On one hand, it activates the endoplasmic reticulum stress pathway, leading to the exposure of calretin (CRT) on the cell membrane and the release of damage-associated molecular patterns (DAMPs) such as ATP and high-mobility group box 1 (HMGB1), thereby promoting the uptake and processing of tumor antigens by dendritic cells (DCs); On the other hand, it induces mitochondrial outer membrane permeability (MOMP), leading to the leakage of mitochondrial DNA (mtDNA) into the cytoplasm, activating the cGAS-STING pathway and significantly upregulating type I interferon (IFN-I) secretion, thereby enhancing the expression level of MHC-I on the surface of tumor cells[9]. Additionally, the mechanism of MHC-I upregulation is closely associated with chemotherapy-induced DNA damage: platinum-DNA adducts formed by oxaliplatin directly generate tumor-specific neoantigens and enhance the activity of antigen processing-related transporters (TAP) and the immunoproteasome by activating the ATM/ATR-Chk1 DNA damage response pathway, thereby significantly improving the presentation efficiency of neoantigen-MHC-I complexes[10].

In the immune recognition process, this dual sensitization (neoantigen release & MHC-I upregulation) produces a cascading amplification effect, where the increased expression of MHC-I-neoantigen complexes lowers the recognition threshold of $CD8^+$ T cells, while oxaliplatin simultaneously reduces the number and function of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), further improving the formation of immune synapses between $CD8^+$ T cells and tumor cells; this process also involves an IFN-γ-mediated positive feedback loop, where activated $CD8^+$ T cells secrete IFN-γ to further upregulate MHC-I expression and recruit more T cell infiltration[11]. The clinical translational value of this intrinsic sensitization mechanism has been confirmed, for example, the combination of axitinib (an anti-angiogenic agent) and pembrolizumab (a PD-1 inhibitor) significantly improved the objective response rate (ORR: 59% vs. 35%) compared to monotherapy[12], indicating that sensitized antigen presentation can effectively overcome the efficacy bottleneck of immune checkpoint inhibitors in monotherapy.

3.3. Metabolic reprogramming and immune regulation

Immunotherapy combined with chemotherapy can reshape the tumor metabolic microenvironment by targeting the IDO/A2AR pathway to synergistically regulate tryptophan/adenosine metabolism, reversing immune suppression and enhancing antitumor effects. The IDO/A2AR dual-target inhibitor simultaneously blocks abnormal tryptophan metabolism and adenosine signaling pathways, alleviating the immunosuppressive state of the tumor microenvironment (TME), significantly enhancing the killing capacity of immune cells, thereby overcoming chemotherapy resistance and enhancing the efficacy of chemotherapy. Zhang Xiaolei's team's research literature[13] further revealed that chemotherapy-resistant non-small cell lung cancer (NSCLC) mouse models were unresponsive to anti-PD-L1 antibodies, confirming that chemotherapy resistance can lead to cross-resistance to immunotherapy[14]. This mechanism is associated with the overexpression of extracellular nucleotidases CD39/CD73 in resistant tumor cells, which catalyze ATP hydrolysis, leading to the accumulation of adenosine in the TME. Tumor-derived adenosine activates the adenosine A2A receptor (A2AR), triggering the PKA/mTOR signaling pathway to reprogram the metabolism of tumor-associated macrophages (TAMs), thereby inducing their high expression of indoleamine 2, 3-dioxygenase 1 (IDO1), which depletes tryptophan and impairs T cell function.

Concurrently, the lactate microenvironment, as a core product of tumor glycolysis (Warburg effect), drives immune evasion through multi-level mechanisms: receptor signaling axis: Lactic acid activates the G protein-coupled receptor GPR81, inhibiting adenylate cyclase (AC) activity and reducing cAMP levels, thereby suppressing PKA activity. This promotes the dephosphorylation and nuclear translocation of the transcription co-activator TAZ, which forms a complex with TEAD1 to directly activate the PD-L1 promoter; Epigenetic modification: Lactic acid-mediated histone lactylation modifies the expression of immune-related genes; Immune cell function inhibition: A high lactate environment directly

inhibits T/NK cell activity. Clinical evidence shows that lactate levels in tumor tissues are positively correlated with PD-L1 expression and significantly associated with poor patient outcomes. Targeted intervention strategies (such as MCT1/4 inhibitors) combined with PD-1/PD-L1 blockers have been shown to have synergistic antitumor effects in experimental models.

In summary, the lactate microenvironment promotes PD-L1 expression through three dimensions: the GPR81/cAMP/TAZ-TEAD1 signaling axis, epigenetic reprogramming, and immune cell function regulation, laying the theoretical foundation for the development of combined therapies targeting lactate metabolism and PD-L1.

3.4. Microbiome-Immunotherapy Axis

The Immune-Oncology-Microbiome (IOM) axis refers to the immune function of the gut microbiota in regulating the tumor microenvironment and systemic immunity. Research has found that beneficial microorganisms such as Bifidobacterium and Ruminococcus are enriched in post-treatment fecal colonies, which helps alleviate inflammatory diseases and metabolic disorders, upregulate CD4+ T cells, and increase the production of short-chain fatty acids, thereby exhibiting antitumor capabilities. Zhang Zhongtao and Yao Hongwei, through literature[15], examined the prognosis of patients after immunotherapy combined with chemotherapy and found that gut core bacteria were enriched in patients who responded well to long-term neoadjuvant chemoradiotherapy combined with immunotherapy, while Bacteroidetes, which induce colorectal cancer, were present in the baseline communities of patients who did not respond to treatment.

Antibiotics can have certain negative effects on clinical response. Their mechanism involves disrupting the intestinal barrier and inducing systemic inflammation. Antibiotics increase intestinal permeability and inhibit the expression of tight junction proteins, leading to the entry of bacterial endotoxins (LPS) and pathogen-associated molecular patterns (PAMPs) into the bloodstream. Additionally, antibiotics can activate the mononuclear phagocyte system to overproduce pro-inflammatory factors such as TNF-α and IL-6, triggering systemic inflammatory responses that counteract the local antibacterial effects of antibiotics. Beta-lactam antibiotics like cefotiam can induce endotoxin release, exacerbating inflammatory damage in sepsis patients[16]. Therefore, clinical treatment should combine microbiota analysis to optimize antibiotic usage strategies and explore interventions such as fecal microbiota transplantation and probiotic supplementation to restore immune microenvironment balance.

3.5. Drug resistance mechanisms and reversal strategies

Immunotherapy combined with chemotherapy has become an important treatment modality for various malignant tumors; however, the emergence of drug resistance significantly limits its clinical efficacy. The mechanisms underlying the emergence of drug resistance primarily involve intrinsic factors of tumor cells, microenvironmental regulation, and host-specific factors. For instance, at the microenvironmental level, the infiltration of immune-suppressive cells (such as Tregs and MDSCs) by the Binnewies team, combined with hypoxia-mediated vascular abnormalities, collectively form an immune-suppressive barrier that impedes drug delivery and immune cell infiltration. Additionally, abnormal signaling pathways (such as MAPK mutations or PTEN deletions) can activate the PI3K-AKT pathway or inactivate interferon-γ (IFN-γ) signaling, thereby weakening T cell killing function[17]. Current clinical strategies to reverse drug resistance primarily include combination therapy and the development of new targets. The synergistic effects of ICIs and chemotherapy have been validated by multiple trials, such as pembrolizumab combined with platinum-based chemotherapy significantly extending progression-free survival in non-small cell lung cancer patients. The addition of radiotherapy can enhance antigen release by inducing immunogenic cell death, while anti-angiogenic drugs (such as bevacizumab) can improve microenvironment hypoxia and enhance T cell infiltration[18]. Future research should further elucidate the spatiotemporal heterogeneity of drug resistance and develop synergistic therapies targeting epigenetic regulation (e.g., DNA methylation inhibitors) or metabolic reprogramming (e.g., IDO inhibitors) to achieve breakthroughs in reversing drug resistance.

3.6. Breakthroughs in new delivery systems

In recent years, the rapid development of nanomedicine delivery systems has provided breakthrough strategies for overcoming resistance to tumor immunotherapy combined with chemotherapy. Multiple research teams[19,20] have achieved multiple synergies through material innovation and structural design, including precise drug delivery, microenvironment regulation, and immune activation. In terms of activating innate immune pathways, Xiao Haihua et al.[21] constructed a multi-modal tetrahedral DNA nanostructure (84bp-tdnisd/56MESS) that simultaneously activates the cGAS-STING pathway by encapsulating platinum-based chemotherapy drugs and stimulating DNA with interferon, achieving synergistic clearance of primary and metastatic tumors in a breast cancer model[22]. Targeting tumor microenvironment-specific responses, Lü Wanliang et al.[23] developed protease-responsive liposomes that leverage the high expression of Legumain protease in colon cancer to achieve on-demand release of anti-PD-L1 antibodies and doxorubicin, forming an "immune activation-chemotherapy killing" closed-loop system[24]. These studies collectively reveal the advantages of nanodelivery systems in reversing drug resistance, including precise spatiotemporal regulation, multi-mechanism synergy, and specific response to the microenvironment.

4. Clinical Translation and Perspectives

Although chemotherapy combined with immunotherapy has demonstrated synergistic potential in various malignant tumors, its individualized clinical application still faces significant challenges. Achieving precision medicine relies on tools that can predict patient treatment responses. Currently, organoids and patient-derived xenograft (PDX) models are key platforms in preclinical research: organoids retain the tissue structure, genetic mutation profile, and drug sensitivity of the primary tumor, providing an ideal system for high-throughput screening of chemotherapy-targeted-immunotherapy combination regimens in vitro[25,26]; while PDX models dynamically simulate tumor microenvironment (TME) characteristics by transplanting patient tumors into immunodeficient mice, with their predictive accuracy for chemotherapy-immunotherapy combination responses (AUC >0.85) significantly outperforming traditional cell lines. Both model types have limitations—organoids lack the immune cell interaction network in the TME, while PDX models cannot fully reconstruct human immune system function due to host immune deficiency. Future efforts should focus on integrating multi-omics data to enhance model predictive efficacy and advancing "organoid/PDX-guided clinical trial" design to accelerate drug development and provide practical evidence for personalized treatment decisions. Toxicity Management Policies

Although immune checkpoint inhibitors (ICIs) combined with chemotherapy can enhance antitumor efficacy, the combined risk of immune-related adverse events (irAEs) and chemotherapy-induced bone marrow suppression significantly increases the difficulty of clinical management. IrAEs (such as myocarditis and pneumonia) may synergistically exacerbate organ damage with chemotherapy toxicity (such as neutropenia), and the existing toxicity warning system has obvious deficiencies. On one hand, there is a lack of organ-specific biomarkers; for example, there are no early serum biomarkers for myocarditis associated with anti-CTLA-4, and by the time cTnI levels rise, the damage is already irreversible. On the other hand, there is a lack of uniform management standards; for example, hormone therapy may exacerbate the risk of chemotherapy-related infections, but discontinuing the therapy may lead to irAE recurrence. Therefore, future efforts should focus on developing dynamic monitoring technologies and establishing multidisciplinary toxicity management teams to optimize treatment safety.

5. Clinical Translation and Perspectives

This paper primarily discusses the multiple mechanisms and clinical translation potential of combining immune checkpoint inhibitors with chemotherapy drugs. Through an analysis of existing literature, it can be observed that chemotherapy drugs significantly enhance the immune system's ability to recognize and eliminate tumors by inducing immunogenic cell

death and altering the tumor microenvironment. The interactions between drug metabolism enzymes and transporters, time-dependent treatment sequencing, dual pathways for immune system activation, intrinsic sensitization of tumor cells, the influence of the microbiome, and strategies to reverse resistance mechanisms all provide theoretical foundations and practical guidance for combination therapy.

In terms of clinical translation, personalized dosing and toxicity management remain major challenges. Organoids and patient-derived xenograft (PDX) models provide powerful tools for predicting treatment responses, but further optimization is needed to better mimic the human immune system. Future research should focus on integrating multi-omics data to develop more precise treatment regimens and optimize treatment safety through dynamic monitoring technologies and multidisciplinary toxicity management teams.

The development of nanomedicine delivery systems also offers new approaches to overcoming drug resistance by precisely regulating drug release and the microenvironment to synergistically combat tumors. In summary, the combination of immune checkpoint inhibitors and chemotherapy drugs demonstrates significant synergistic potential in various malignant tumors, but further research and optimization are needed for broader clinical application.

Disclosure statement

The author declares no conflict of interest.

References

[1] Garassino M C, Gadgeel S, Speranza G, 2023, Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. J Clin Oncol. 41(11):1992-1998. doi: 10.1200/JCO.22.01989.

[2] Nogami N, Barlesi F, Socinski M A, 2022, IMpower150 Final Exploratory Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in Key NSCLC Patient Subgroups With EGFR Mutations or Metastases in the Liver or Brain. J Thorac Oncol. 17(2):309-323. doi: 10.1016/j.jtho.2021.09.014.

[3] Liu J, 2012, Cytochrome P450 activity and cancer treatment. Drug Evaluation, 9(05): 14-18.

[4] Huo Y, Wang D, Yang S, 2024, Optimal timing of anti-PD-1 antibody combined with chemotherapy administration in patients with NSCLC. J Immunother Cancer. Dec 19; 12(12):e009627. doi: 10.1136/jitc-2024-009627.

[5] Obeid M, Tesniere A, Ghiringhelli F, 2007, Calreticulin exposure dictates the immunogenicity of cancer cell death. Nat Med. 13(1):54-61. doi: 10.1038/nm1523. Epub 2006 Dec 24.

[6] Tournant F, 2023, Stromal cells drive tumorigenesis in BRCA1 mutation carriers. Nat Rev Cancer. 23(6):349. doi: 10.1038/s41568-023-00580-8.

[7] Li Z, Lai X, Fu S, 2022, Immunogenic Cell Death Activates the Tumor Immune Microenvironment to Boost the Immunotherapy Efficiency. Adv Sci (Weinh). 9(22):e2201734. doi: 10.1002/advs.202201734.

[8] Zhou X, Hou W, Gao L, 2020, Synergies of Antiangiogenic Therapy and Immune Checkpoint Blockade in Renal Cell Carcinoma: From Theoretical Background to Clinical Reality. Front Oncol. 10: 1321. doi: 10.3389/fonc.2020.01321.

[9] Ahmed A, Tait S W G, 2020, Targeting immunogenic cell death in cancer. Mol Oncol. 14(12):2994-3006. doi: 10.1002/1878-0261.12851.

[10] Łuksza M, Sethna Z M, Rojas L A, 2022, Neoantigen quality predicts immunoediting in survivors of pancreatic cancer. Nature. 2022 Jun;606(7913):389-395. doi: 10.1038/s41586-022-04735-9.

[11] Mehdipour P, Marhon S A, Ettayebi I, 2020, Epigenetic therapy induces transcription of inverted SINEs and ADAR1 dependency. Nature. 588(7836):169-173. doi: 10.1038/s41586-020-2844-1.

[12] Yang Z, Ma J, Han J, 2024, Gut microbiome model predicts response to neoadjuvant immunotherapy plus

chemoradiotherapy in rectal cancer. Med. 5(10):1293-1306.e4. doi: 10.1016/j.medj.2024.07.002.

[13] Ding W, Mo J, Su Y, 2025, Metabolic reprogramming of tumor-associated macrophages via adenosine-A2AR signaling drives cross-resistance in non-small cell lung cancer. Drug Resist Update. 82:101272. doi: 10.1016/j.drup.2025.101272.

[14] Xie J, Liu M, Deng X, 2024, Gut microbiota reshapes cancer immunotherapy efficacy: Mechanisms and therapeutic strategies. Imeta. 3(1):e156. doi: 10.1002/imt2.156.

[15] Gao J, Gu X, Pang M, 2024, RHC-SNAPSHOT investigators. Risk factors for anastomotic leak and postoperative morbidity after right hemicolectomy for colon cancer: results from a prospective, multi-centre, snapshot study in China. Br J Surg. 111(1):znad316. doi: 10.1093/bjs/znad316.

[16] Wang T T, Zeng H H, Hu T, 2024, Predictive value of pan-immunological inflammation scores for primary resistance to immunotherapy combined with chemotherapy in HER-2-negative advanced gastric cancer. Journal of Jinzhou Medical University, 45(06): 31-36. DOI: 10.13847/j.cnki.lnmu.2024.06.002.

[17] Wu Q, Yang Z, Nie Y, 2014, Multi-drug resistance in cancer chemotherapeutics: mechanisms and lab approaches. Cancer Lett. 347(2):159-66. doi: 10.1016/j.canlet.2014.03.013.

[18] Fan D, Cao Y, Cao M, 2023, Nanomedicine in cancer therapy. Signal Transduct Target Ther. 8(1):293. doi: 10.1038/s41392-023-01536-y.

[19] Ezike T C, Okpala U S, Onoja U L, 2023, Advances in drug delivery systems, challenges and future directions. Heliyon. 9(6):e17488. doi: 10.1016/j.heliyon.2023.e17488.

[20] Wang X Y, Fu S J, Meng X J, 2024, Research Progress on New Methods and Technologies for Analyzing the In Vivo Fate of Nanodrug Delivery Systems. Progress in Pharmacy, 48(10): 747-760. DOI: 10.20053/j.issn1001-5094.2024.10.004.

[21] Zhang L, Wang Y, Karges J, 2023, Tetrahedral DNA Nanostructure with Interferon Stimulatory DNA Delivers Highly Potent Toxins and Activates the cGAS-STING Pathway for Robust Chemotherapy and Immunotherapy. Adv Mater. 35(8):e2210267. doi: 10.1002/adma.202210267.

[22] Yang Z, Gao D, Zhao J, 2023, Thermal immuno-nanomedicine in cancer. Nat Rev Clin Oncol. 20(2):116-134. doi: 10.1038/s41571-022-00717-y.

[23] Liu Y, Xie Y, Chen Y, 2025, A protease-cleavable liposome for co-delivery of anti-PD-L1 and doxorubicin for colon cancer therapy in mice. Nat Commun. 16(1): 2854. doi: 10.1038/s41467-025-57965-6.

[24] Fan D, Cao Y, Cao M, 2023, Nanomedicine in cancer therapy. Signal Transduct Target Ther. 8(1):293. doi: 10.1038/s41392-023-01536-y.

[25] Yu W D, Sun G, Li J, 2019, Mechanisms and therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy. Cancer Lett. 452: 66-70. doi: 10.1016/j.canlet.2019.02.048.

[26] Pointer K B, Pitroda S P, Weichselbaum R R, 2022, Radiotherapy and immunotherapy: open questions and future strategies. Trends Cancer. 8(1):9-20. doi: 10.1016/j.trecan.2021.10.003.