Biomedical Data Science
2025, VOL. 5, NO. 3, 125-129
DOI: 10.47297/wspbdsWSP2752-630525.20250503

Multi-Target Synergistic Fight Against Cancer: Mechanism Exploration And Breakthroughs Under The Perspective Of Systems Biology

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ABSTRACT
Despite the discovery of a large number of cancer-related targets in recent years, no prevention or treatment relying on a single target has ever been able to rank as a panacea, and although all of these targets have demonstrated their superiority, multi-target synergization is clearly more effective than single application. This study demonstrates that synergistic strategies integrating the four dimensions of metabolic reprogramming, immune microenvironment remodeling, epigenetic intervention, and colony-host interactions can effectively overcome drug resistance; however, bypass activation, spatiotemporal heterogeneity, and delivery efficiency remain challenges; in the future, it will be necessary to develop intelligent models to quantify synergism, innovate delivery technologies to achieve spatiotemporal controlled release, and deepen the 'epi-immune-metabolism' integration therapy to promote eradication. In the future, it is necessary to develop intelligent model quantitative synergy, innovative delivery technology to realize spatiotemporal controlled release, and deepen 'epi-immune-metabolic' integrated therapy to promote radical breakthrough.

KEYWORDS
Multi-targeted synergistic therapy; Metabolic reprogramming; Tumor immune microenvironment; Epigenetic intervention; Colony-host interactions

1 Mechanisms of action of multi-target synergies

1.1 Metabolic reprogramming and energy deprivation5

Metabolic reprogramming is a core strategy for cancer cells to adapt to the microenvironment, which is characterized by a shift in energy metabolism pattern, enhanced biosynthesis and dynamic adjustment of mitochondrial function. Energy acquisition reprogramming is characterized by 1) Warburg effect (dominated by aerobic glycolysis), which supports proliferation through rapid generation of ATP and metabolic intermediates, and 2) glutamine metabolism dependence, which relies on glutamine catabolism to replenish metabolic intermediates to sustain biosynthesis. Enhanced anabolism then meets malignant proliferative demands through lipid and nucleic acid synthesis pathways (e.g., fatty acid synthase activation). Mitochondrial functional remodeling is reflected in the difference in metabolic phenotypes between primary and metastatic foci: metastatic cancer cells tend to resist stress through oxidative phosphorylation, whereas dormant cells rely on mitochondrial metabolism for survival. This process is mediated by classical pathways such as PI3K/Akt/mTOR, which dominate the phenotypic switch by regulating glucose uptake and metabolic enzyme expression, making it an important direction for targeted intervention.

Cancer cells construct systemic adaptive networks through the "metabolic-immune axis". Metabolites (e. g. lactate) induce immune checkpoint protein expression and inhibit T cell function, forming an immune escape barrier. This bi-directional regulation allows cancer cells to maintain a survival advantage despite metabolic stress, suggesting the limitations of single pathway targeting. For example, mTOR inhibitors block glucose metabolism but may trigger compensatory mechanisms, whereas combination strategies (e. g., metformin with immunotherapy) enhance efficacy through simultaneous deprivation of energy supply and deregulation of immunosuppression.

In addition, metabolic reprogramming interacts with distal regulatory systems. Gut flora metabolites (e.g., butyric acid) can influence the metabolic phenotype of cancer cells through epigenetic modifications, providing new targets for cross-system interventions. The current study emphasizes the need to integrate the "metabolism-immunity-flora" multidimensional strategy to break the compensatory network through time-sequenced combinatorial interventions.

1.2 Immune microenvironment remodeling9

Tumor microenvironment (TME) is a dynamic system composed of tumor cells, immune cells, stromal components and abnormal metabolites, characterized by immunosuppression, metabolic disorders and physical barriers. Since the breakthrough of immune checkpoint inhibitors and CAR-T therapies, research has gradually revealed that multidimensional intervention is the core strategy for remodeling the TME. Currently, microenvironment remodeling focuses on three major directions: 1) immune checkpoint blockade to relieve T-cell suppression; 2) vascular normalization (e. g., anti-VEGF therapies) to transiently improve perfusion and drug delivery; and 3) stromal barrier softening (e. g.,

targeting CAFs or degradation of ECM) to promote immune infiltration. The clinical value of synergistic strategies has been validated in the treatment of hepatocellular carcinoma: combination regimens of PD-L1 inhibitors with anti-angiogenic agents significantly enhance efficacy through multi-target synergy.

The limitations of immunotherapy stem in part from the epigenetic regulation of TME. Tumor cells rebuild epigenetic inhibitory networks after immune checkpoint inhibition through mechanisms such as methylation of interferon-associated genes, creating adaptive resistance. This highlights the multidimensional defense properties of cancer cells, which need to be broken by cross-scale interventions for synergistic regulation. For example, epigenetic drugs such as decitabine can simultaneously reverse the silencing of DNA repair genes and deregulate Treg cell function, realizing "epi-immune" dual-targeting synergy. Such strategies can block the compensatory pathway of cancer cells by simultaneously interfering with genomic stability and the immune microenvironment.

In conclusion, TME remodeling requires the integration of a multidimensional strategy of immune activation-vascular modulation-epidemiologic intervention. Research trends indicate that 1) precise identification of key nodes (e. g., the interaction between metabolic abnormalities and physical barriers); 2) development of time-sequenced combinations (e. g., combined immunotherapy during the window period of vascular normalization); and 3) exploration of cross-systems regulation (e.g., the influence of colony metabolites on epitope modification) will become an important direction to break through the current therapeutic bottlenecks.

1.3 Epigenetic and DNA repair7

Epigenetic interferes with DNA damage repair (DDR) through three major pathways: DNA methylation, histone modification and non-coding RNAs, driving genomic destabilization. hypermethylation of the BRCA1 promoter silences its transcriptional activity, leading to defective homologous recombination repair (HRR) and forcing tumor cells to turn to the error-prone non-homologous end-joining (NHEJ) mechanism; histone deacetylase (HDAC) aberrant activation induces chromatin tightening and hinders the recruitment of repair complexes such as ATM/Rad51 to the damage site by decreasing histone acetylation levels; and non-coding RNAs (e.g., miR-182) affect PARP inhibitor sensitivity by regulating BRCA1 expression.

Significant progress has been made in intervention strategies targeting the epi-DDR interaction network. DNA methyltransferase inhibitors (DNMTi, e. g., decitabine) reverse the aberrant methylation of genes such as BRCA1 and MGMT, restoring their transcriptional activity, and creating a synthetic lethal effect with PARP inhibitors (olaparib) [9], which is a regimen that has been shown to be highly efficacious in BRCA-mutant breast cancer. Histone deacetylase inhibitors (HDACi, e. g., vorinostat) enhance damage signaling by radiotherapy/chemotherapy by increasing histone acetylation levels and elevating chromatin accessibility of repair genes, such as ATM and CHK1, while up-regulating pro-apoptotic proteins (Bax, Puma) [9] synergistically inducing cell death. DNMTi activates endogenous viral signaling pathways, which are synergistically induced with immune checkpoint inhibitors synergistically.

However, single-target epitope interventions face multiple challenges. Redundancy in the repair network leads to compensatory resistance: while HDACi enhances ATM expression to promote double-strand break (DSB) repair, it may simultaneously activate DNA-PKcs, a key factor of the NHEJ pathway; EZH2 inhibitors (tazetostat) restore BRCA1 expression by inhibiting H3K27me3 [9], but tumor cells can remodel the epigenetic landscape. In addition, aberrant methylation of DNMT3A in tumor stem cells (CSCs) silences the antioxidant gene ALDH1A1, but impaired drug penetration due to microenvironmental hypoxia limits their therapeutic response.

Breaking through the above dilemma requires the development of multidimensional synergistic strategies. Combining DNMTi with EZH2 inhibitor can synchronously release the multi-layer inhibition of repair genes by DNA methylation and H3K27me3; HDACi in combination with BET inhibitor can block the interaction between acetylated histones and BRD4, and inhibit the activity of pro-repair transcription factor MYC. For IDH1-mutant tumors, combining IDH1 inhibitors with DNMTi can reverse repair gene silencing while enhancing genomic stability through metabolic reprogramming. Intelligent nanodelivery systems (e. g., liposome-encapsulated drugs) can achieve spatiotemporal synergistic release of epimers and DDR inhibitors, enhancing targeting and reducing toxicity.

In conclusion, the multilevel nature of the epigenetic-DDR interaction network requires a cross-dimensional therapeutic strategy. The integration of the three-dimensional synergistic scheme of "epigenetic reprogramming + reparative intervention + intelligent delivery" can effectively overcome drug resistance and realize precise treatment through the dynamic regulation of metabolic-immune-epigenetic network. This framework lays the theoretical foundation for exploring the chemical biological mechanism of the multidimensional synergistic network.

1.4 Distal regulation mediated by intestinal flora10

Gut flora (GM) constitutes a multidimensional regulatory network through metabolites, immune modulation and epigenetic modifications, which profoundly affects cancer progression and therapeutic response. Dysbiosis can lead to

overproliferation of pathogenic bacteria (e.g., Clostridium difficile), which drives colorectal cancer development through pro-inflammatory microenvironment formation and immunosuppressive mechanisms, and its pro-carcinogenic effects can be manifested as 1) promoting cancer cell proliferation (activation of oncogenic signaling pathways); 2) inducing chemoresistance (modulation through autophagy pathways); and 3) destroying the intestinal barrier (activation of epithelial mesenchymal transition). Probiotic metabolites such as short-chain fatty acids (SCFAs), on the other hand, reverse oncogene silencing through epigenetic modifications (e. g., histone acetylation) and synergize with immunotherapy to enhance antitumor responses.

The synergistic effects of colony remodeling and immunotherapy have been demonstrated: Bifidobacterium bifidum enhances T-cell infiltration through metabolic modulation], and Acinetobacter spp. enhances the efficacy of PD-1 inhibitors through the modulation of immune cell function. This "metabolic-immune" synergistic strategy provides new directions to overcome drug resistance, such as fecal microtransplantation (FMT) combined with immune checkpoint inhibitors to reverse PD-1 treatment resistance, and dietary fiber to remodel the ecology of the bacterial flora through SCFAs and metabolically synergize with metformin.

Current challenges focus on the spatiotemporal heterogeneity of flora: functional differences between mucosal and fecal flora, and uncertainties in individualized response mechanisms, hindering the development of precise intervention strategies [14]. Breakthrough directions include 1) resolving the core nodes of colony-host dynamic interactions, 2) developing regulatory tools targeting specific metabolic pathways, and 3) establishing a framework for individualized therapy based on colony typing. These advances will promote the transformation of GM from "association research" to "mechanism intervention", and ultimately realize the multidimensional synergistic regulation of cancer treatment.

2 Design and optimization of synergistic combinations

2.1 Combination strategy based on pathway complementarity13

Multi-targeted synergistic therapies achieve efficacy gains (1+1>2) through simultaneous intervention in a network of functionally interoperable targets, which is centered on the structural fitness of targets and the dynamic coupling of signaling networks. Disease complexity drives strategy innovation: cancer drug resistance involves the activation of compensatory pathways (e. g., compensatory upregulation of other pathways after EGFR inhibition), while metabolic dysregulation requires cross-dimensional interventions (cross-regulation of lipid metabolism and inflammatory pathways) . Based on the metabolic-immune-epigenetic network resolution (Sections 2.1-2.3), vertical synergies need to target upstream and downstream of the same pathway (e.g., the combination of epigenetic drugs and targeted therapies in the DNA damage repair pathway), and horizontal synergies need to be complementary across dimensions (e. g., immune checkpoint blockade combined with bacterial colony remodeling strategies).The structural classification of CATH-FunFams reveals the characteristics of the conserved target family, empowering multi target drug design; chemical language modeling (CLM) breaks through the limitations of single-molecule multi-target ligands, such as FXR/sEH dual inhibitors showing high activity characteristics; CRISPR screening combined with network pharmacology systematically identifies synergistic target combinations, which significantly improves the efficiency of product synthesis by remodeling metabolic pathways. In terms of combinations upstream and downstream of the same pathway, the combination of gefitinib (EGFR inhibition) and trametinib (MEK inhibition) significantly enhanced efficacy and prolonged clinical survival. The current challenges focus on dynamic network modeling (drug resistance mutation-induced target network reconstruction) and clinical translation bottlenecks (optimization of multi-target delivery efficiency). In the future, we will rely on single-cell multi-omics to analyze spatio-temporal synergistic mechanisms, integrate AI tools to improve the accuracy of synergistic target prediction, develop structure-function dual-driven ligands, and construct a "precise blocking-dynamic regulation" synergistic paradigm. We will develop structure-function dual-driver ligands to build a "precise blocking-dynamic regulation" synergy paradigm.

2.2 Dose-Time Dependent Effects8

In cancer combination therapy, the nonlinear relationship between dose and time has an important impact on efficacy. It has been shown that the antianginal effect of Danhong injection (DHI) peaks at mid-intervention, but declines in subsequent use, which is closely related to the compensatory activation of metabolic pathways. This "rise-plateau-decline" kinetic profile suggests that a sustained low-dose strategy may result in epigenetic regulation by maintaining steady-state serum concentrations, but may trigger feedback inhibitory mechanisms, whereas an intermittent high-dose regimen may break through the barrier of the first-pass effect to directly inhibit the key inflammatory pathways, but is associated with a dose-dependent risk of hepatotoxicity.

Microbial engineering studies further revealed the temporal regulatory mechanism of multi-target synergistic intervention. In the Bacillus subtilis fermentation system, synchronized inhibition of lipid metabolism-related genes and

transporter proteins significantly enhanced the efficiency of surfactin biosynthesis, and its non-ribosomal peptide synthesis genes were maintained at a high expression level throughout the fermentation. This time-dependent amplification effect is directly related to the temporal control of key precursors: timely supplementation of precursors can effectively enhance the end-product yield, while delayed supplementation loses the synergistic effect. The results suggest that precise timing of intervention at metabolic nodes is decisive for optimizing the biosynthetic pathway.

2.3 Innovations in delivery technology7

Based on cutting-edge research, breakthroughs in delivery technologies are reshaping the boundaries of efficacy of combination therapies. In terms of nanocarrier systems, curcumin liposomes (Eudragit L100-55 encapsulated) can significantly enhance bioavailability. Even more innovative is the exosome delivery technology - engineered exosomes loaded with drugs have dramatically improved the efficiency of blood-brain barrier penetration and demonstrated significant tumor suppression in glioma models. The intelligent response system for the intestinal microenvironment controls the pH gradient to achieve the sequential release of vitamins and metabolic precursors: the antacid layer in the stomach stabilizes and protects the drug, the ileum releases the vitamins accurately, and the colon enzymatically cleaves the resistant starch to produce butyric acid and regulate the balance of the bacterial flora.

In industrial translation, microfluidic technology breaks through the traditional limitations and significantly optimizes the particle size uniformity and production cost of nanoparticles. However, long-term toxicity assessment reveals that the carrier material may cause organ fibrosis risk, suggesting the need to develop novel lyophilization protection systems to maintain the stability of drug delivery. Currently, the bottleneck of research focuses on individualized adaptation strategies, and genotype-based delivery system dosing schemes can significantly increase drug exposure in patients with specific metabolic phenotypes, laying the foundation for precision therapy.

Chapter III: Challenges and future directions

The central challenge for multi-targeted synergistic therapies stems from the complexity and dynamic adaptability of living systems. At the scientific level, the redundancy of metabolic-immune-epigenetic networks leads to the frequent occurrence of compensatory drug resistance - single pathway inhibition often triggers bypass activation or epigenetic remodeling, which undermines efficacy. Meanwhile, the spatial and temporal heterogeneity of the tumor microenvironment (e.g., metabolic phenotypic shifts, fluctuating flora composition) and individual differences make the response to intervention unpredictable. Existing delivery systems are limited by the efficiency of biological barrier penetration and long-term safety issues, which restrict the precise delivery of multi-target drugs.

Technical bottlenecks focus on the practical barriers to synergistic strategies: the need for multi-drug time-controlled release is in conflict with the limitations of current delivery technologies; dose optimization lacks dynamic monitoring tools, continuous dosing is prone to feedback inhibition, and intermittent dosing is difficult to match the time window of immunotherapy.

Future breakthroughs need to focus on three areas:

Intelligent computation-driven: fusion of multi-omics data to construct dynamic network models and quantify target interaction thresholds to predict optimal synergistic solutions;

Innovations in precision delivery: development of biomimetic carriers for spatio-temporally resolved drug release, breaking the biological barrier and reducing systemic toxicity;

Cross-dimensional synergistic paradigm: integrating epigenetic reprogramming, metabolic intervention and immune activation to enhance therapeutic depth through multidimensional interplay mechanisms.

Conclusion: Only by integrating intelligent design, precise delivery and dynamic regulation with a systemic perspective can we realize the leap of multi-target synergy from empirical combination to mechanism-driven.

3 Conclusions and outlook

With innovations in multi-omics technologies, artificial intelligence and delivery systems, multi-targeted synergistic therapy has become a central strategy to overcome tumor complexity. By integrating metabolic reprogramming, immune microenvironment regulation, epigenetic intervention and colony-host interactions networks, this strategy significantly breaks through the drug resistance limitations of single-targeted therapy. However, individual response differences due to tumor heterogeneity, compensatory escape triggered by biological network redundancy, and the efficiency bottleneck of cross-dimensional drug delivery remain key challenges. Future research needs to deeply integrate systems biology, computational science and materials science: on one hand, develop intelligent models to quantify target synergy thresholds for precise patient typing and regimen optimization; on the other hand, innovate biomimetic delivery technologies to achieve spatially and temporally resolved drug synergistic release. Multidisciplinary intersection will promote the clinical translation of "metabolic-immune-epigenetic" triple-track therapies, and ultimately achieve the goal

of tumor eradication with controllable toxicity.

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