Integrative Network Pharmacology and Metabolomics Reveal the Anti-Tumor Mechanisms of Natural Compounds via HIF-1α-Mediated Glycolysis Reprogramming

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Abstract: This study investigates the anti-tumor mechanisms of natural compounds through hypoxia-inducible factor-1α (HIF-1α)-mediated glycolysis reprogramming by integrating network pharmacology and metabolomics. Utilizing multi-omics approaches, we mapped compound-target interactions and metabolic flux alterations in tumor models, revealing that natural compounds suppress HIF-1α signaling and downstream glycolytic enzymes (e.g., HK2, LDHA), thereby disrupting ATP production and lactate accumulation. Functional validation demonstrated that these compounds synergistically inhibit tumor proliferation and metastasis while enhancing chemosensitivity.

***Keywords*:** natural compounds; HIF-1α; glycolysis reprogramming; network pharmacology-metabolomics integration

1. Introduction

Cancer remains a global health challenge due to the limitations of conventional therapies, including drug resistance and systemic toxicity. In recent years, natural compounds have garnered significant attention as potential anti-tumor agents owing to their multi-target therapeutic properties and reduced side effects. However, the precise mechanisms underlying their efficacy, particularly in modulating tumor metabolic reprogramming, remain poorly understood. The Warburg effect, characterized by hypoxia-inducible factor 1α (HIF-1α)-mediated glycolysis even under aerobic conditions, is a hallmark of cancer metabolism that fuels tumor progression, metastasis, and therapeutic resistance[1].

2. Research Status of HIF-1α-Mediated Glycolytic Reprogramming in Cancer Treatment

2.1 Molecular Mechanisms of the HIF-1α Signaling Pathway and Cancer Metabolic Reprogramming

HIF-1α, a master regulator of cellular adaptation to hypoxia, drives tumor metabolic reprogramming by orchestrating glycolytic enzyme expression. Under hypoxia, HIF-1α escapes von Hippel-Lindau (VHL)-mediated proteasomal degradation, heterodimerizes with HIF-1β, and binds hypoxia-response elements (HREs) in target gene promoters. Key glycolytic genes activated by HIF-1α include glucose transporters (GLUT1/3), hexokinase 2 (HK2), phosphofructokinase (PFKFB3), and lactate dehydrogenase A (LDHA), collectively enhancing glucose uptake and lactate production[2].

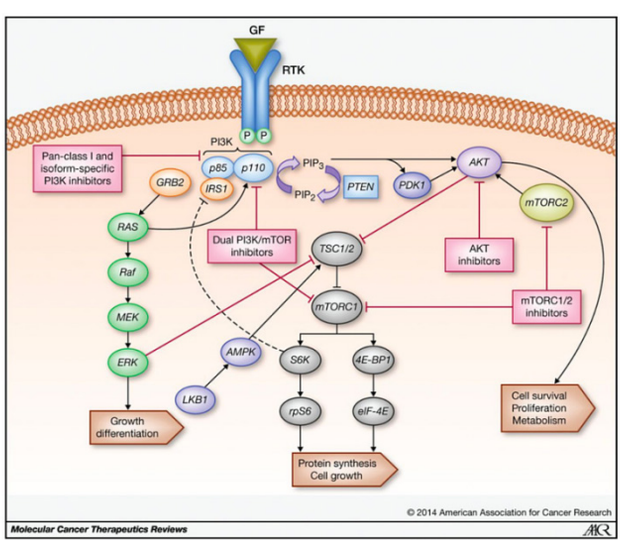

Figure 1. HIF-1α-Mediated Glycolytic Reprogramming in Tumors

2.2 Research Progress on the Regulation of Tumor Glycolysis by Natural Compounds

Natural compounds, such as curcumin, quercetin, and resveratrol, have demonstrated potent anti-glycolytic effects by targeting HIF-1α signaling and key glycolytic enzymes. Polyphenols (e.g., epigallocatechin-3-gallate) inhibit HIF-1α stabilization via PI3K/AKT/mTOR pathway suppression, reducing GLUT1-mediated glucose uptake. Alkaloids like berberine downregulate HK2 and LDHA expression, blocking lactate production and ATP synthesis. Flavonoids (e.g., apigenin) disrupt HIF-1α-DNA binding, impairing transcription of glycolytic genes. Terpenoids (e.g., artesunate) synergistically suppress PDK1, restoring mitochondrial oxidative phosphorylation[3].

3. Key Issues in the Current Research on the Antitumor Mechanisms of Natural Compounds

3.1 Limitations of Targeted Therapy Caused by the Dynamic Regulation of HIF-1α and Tumor Heterogeneity

The efficacy of HIF-1α-targeted therapies is hindered by its context-dependent activation and tumor heterogeneity. HIF-1α levels fluctuate dynamically with oxygen tension, nutrient availability, and oncogenic signals, driven by post-translational modifications (e.g., phosphorylation, acetylation) and crosstalk with stromal cells. Spatial and temporal variations in tumor hypoxia create distinct HIF-1α activity gradients, enabling subpopulations of cancer cells to evade inhibition. Intratumoral heterogeneity further complicates targeting, as clones with divergent HIF-1α expression or mutations in upstream regulators (e.g., VHL, PHDs) exhibit differential glycolytic dependencies. Moreover, compensatory mechanisms (e.g., HIF-2α upregulation, antioxidant pathway activation) allow tumors to bypass HIF-1α suppression[4].

3.2 Inadequate Analysis of the Synergistic Mechanism of Multiple Components of Natural Compounds

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3.3 Lack of Standardized Methods for the Integrated Analysis of Metabolomics and Network Pharmacology

Current integration of metabolomics and network pharmacology lacks standardized protocols, leading to inconsistent data interpretation. Disparate platforms generate non-uniform metabolite profiles, while network tools (Cytoscape vs. STRING) yield variable compound-target networks. Divergent preprocessing methods and pathway enrichment algorithms (KEGG vs. Reactome) introduce bias. Additionally, validation frameworks for correlating metabolic shifts with network-predicted targets are absent, undermining mechanistic confidence.

4. Antitumor Strategies of Natural Compounds Based on Multi-Omics Integration

4.1 Development of Dynamic Tracking Technology for Key Targets of HIF-1α-Mediated Glycolysis

Advanced live-cell imaging and CRISPR-based biosensors enable real-time monitoring of HIF-1α dynamics under hypoxia. Single-cell RNA-seq and spatial metabolomics map spatiotemporal variations in glycolytic targets (e.g., LDHA, PDK1) across tumor subregions. Photoactivatable probes (e.g., HaloTag-HIF-1α) quantify protein degradation rates, while FRET-based sensors track ATP/lactate flux. These technologies resolve HIF-1α's transient activation and heterogeneous metabolic dependencies, guiding precision targeting.[5].

4.2 Construction of a Multidimensional Analysis Framework for the Natural Compound-Target-Metabolic Network

Integrate network pharmacology (STITCH, SwissTargetPrediction) with metabolomics (pathway enrichment, flux balance analysis) via AI-driven platforms. Deep learning models (e.g., GNNs) predict compound-target interactions, while multi-omics databases (HMDB, KEGG) link perturbations to metabolic outcomes. Spatial transcriptomics and lipidomics add tissue-context specificity, creating 3D interaction maps. This framework deciphers system-level actions of natural

compounds across hypoxic/normoxic niches.

4.3 Synergistic Verification of Metabolic Reprogramming Markers and Pharmacodynamic Biomarkers

Cross-validate metabolomic signatures (e.g., lactate/NADPH ratios) with pharmacodynamic endpoints (tumor volume, Ki-67) using machine learning. Identify co-varying biomarkers (e.g., HIF-1α↓ + LDHA↓ + ATP↓) through LASSO regression in preclinical models. Organoid-based co-cultures and PDX models test biomarker robustness under hypoxia. AI-driven meta-analysis correlates metabolic shifts (GC-MS data) with clinical outcomes, ensuring translatability. Multi-center cohort studies and longitudinal sampling validate biomarker stability across diverse patient populations and treatment phases..

5. Conclusion

This study demonstrates that integrating network pharmacology and metabolomics effectively deciphers the anti-tumor mechanisms of natural compounds via HIF-1α-mediated glycolysis reprogramming. By mapping compound-target-metabolic networks, we reveal their multi-target actions in suppressing glycolytic enzymes, restoring mitochondrial function, and disrupting hypoxic adaptation.

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