ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

LETTER TO EDITOR

Metabolic reprogramming: A key mechanism underlying chemotherapy resistance in non-small cell lung cancer

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To the Editor,

The recent review of Peixoto *et al.* describing altered patterns of chemotherapy resistance in non-small cell lung cancer (NSCLC) was of particular interest to us.[1] They elaborated on the genetic and epigenetic drivers of chemoresistance. In our view, a substantial metabolic overhaul deserves a thorough explanation. As clinicians trained in both traditional Chinese medicine (TCM) and conventional therapy, we have observed NSCLC tumor cells adopting a Warburg-like metabolic signature. This metabolic change drives rapid cancer growth and protects tumor cells from the cytotoxic effects of cisplatin, paclitaxel, and other chemotherapies. In our opinion, specifically targeting the metabolic adaptations in cancer cells is not merely experimental but holds tangible clinical potential. Future studies should involve combination treatment regimens that pair metabolic inhibitors with metabolically active TCM components. These therapies may reduce cancer cell energy production and impede their antioxidant defense mechanisms, thereby enhancing the efficacy of chemotherapeutic regimens. Understanding the metabolic pathways underlying drug resistance can help avoid the pitfalls of a one-size-fits-all approach to chemotherapy and enable metabolism-guided personalized therapy in NSCLC.

The Warburg effect, characterized by increased aerobic glycolysis, appears to be a purposeful evolutionary adaptation for cancer cells instead of an incidental metabolic trait. Exposure to cytotoxic agents results in severe oxidative stress and extensive DNA damage in tumor cells. To cope with this oxidative stress, tumor cells shift toward a glycolysis-dependent program, which helps maintain a high reduced-to-oxidized glutathione ratio, a critical antioxidant buffer[2] that supports the opportunistic removal of reactive oxygen species formed during chemotherapy at the expense of compromised cytotoxicity of the drug introduced.

Additionally, lactic acid, the major metabolic byproduct secreted by cancer cells that depend on glycolysis, acidifies the tumor microenvironment. This acidic milieu not only impairs the effector functions of infiltrating immune cells but also disrupts the pharmacokinetics of weakly basic chemotherapeutic compounds, thereby diminishing their intracellular accumulation in malignant cells.[3]

Emerging evidence indicates that some chemotherapy-resistant NSCLC cells exhibit increased oxidative phosphorylation (OXPHOS), in contrast to the Warburg

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Citation: Zhao C, Wu T, Li Z, Kong X. Metabolic reprogramming: A key mechanism underlying chemotherapy resistance in non-small cell lung cancer. *Eurasian J Med Oncol*. 2026;10(3):026030034. doi: 10.36922/EJMO026030034

Received: January 16, 2026

Accepted: January 19, 2026

Published online: February 20, 2026

effect.[4] Mitochondria are the major sites where adenosine triphosphate is produced, supplying energy for nuclear DNA damage repair. Furthermore, mitochondrial metabolism is closely linked to apoptotic regulation. Drug-resistant cancer cells often exhibit altered mitochondrial fusion–fission dynamics and increased expression of anti-apoptotic proteins such as B-cell lymphoma 2, which reduce their susceptibility to drug-induced cell death.

Targeting metabolic plasticity is therefore crucial for overcoming chemotherapy resistance. Cancer stem cells (CSCs), which are hypothesized to drive tumor recurrence, have the ability to switch from glycolysis to OXPHOS in response to microenvironmental stress.[5] Chemotherapy may selectively enrich quiescent and OXPHOS-dependent CSCs that survive treatment and subsequently fuel tumor regrowth.

Based on our clinical experience, selected TCM formulations can exert tumor-suppressive effects by increasing the activity of immune cells in the host.[6] Preclinical studies show that the bioactive constituents of these herbs, such as ginsenosides and astragaloside IV, may exert synergistic antitumor actions by reversing the Warburg phenotype commonly observed in cancer cells.[7] Specifically, these agents may inhibit rate-limiting enzymes of the glycolytic pathway (e.g., hexokinase 2 and lactate dehydrogenase A), thereby limiting aerobic glycolysis while simultaneously activating mitochondrial apoptotic signaling. This two-pronged action may ultimately sensitize tumor cells to chemotherapy.

Funding

This work was supported by the Science and Technology Development Fund of Tianjin Education Commission for Higher Education (Grant no: 2022KJ180).

Conflict of interest

Xianbin Kong is an Editorial Board Member of this journal but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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