Acta Pharmaceutica Sinica B 2024;14(10):4619–4621

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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HIGHLIGHT

Nanotechnology-based tumor metabolic reprogramming: Insights into nutrient-delivery and metabolism reactivation therapy

KEY WORDS

Metabolic therapy;
Metabolic reprogramming;
Cancer metabolism;
Metabolism reactivation therapy;
Melanin metabolism;
Nutrient-delivery;
Tumor therapy;
Nanotechnology

Metabolic reprogramming in cancer is not only a core hallmark but also exposes treatment vulnerabilities. Several key processes required for tumor initiation and progression—continuous self-renewal, survival, and proliferation—are known to be under metabolic control[1]. Therapeutic opportunities arise from dysregulated metabolism and metabolic crosstalk, as tumor cells become heavily dependent on specific metabolic pathways such as glucose, amino acid, and fatty acid metabolism, as well as nucleotide synthesis[2]. However, many anti-metabolite drugs, including glycolysis inhibitors, have not been successfully applied in clinical settings due to their low specificity and undesirable side effects.

In the June 2024 issue of *Nature Nanotechnology*, Chen et al.[3] reported a nutrient-based metabolic reactivation strategy by constructing L-tyrosine-oleylamine nanomicelles (MTyr–OANPs) to supplement L-tyrosine (Tyr) for the treatment of melanomas (Fig. 1). Their study elucidated the following finding about nutrient-delivery and metabolism reactivation therapy for melanoma: 1. Melanogenesis metabolism is suppressed in advanced skin cutaneous melanoma (SKCM), as demonstrated by single-sample gene set enrichment analysis (ssGSEA) of the gene signature from The Cancer Genome Atlas (TCGA) in SKCM patients. 2. The L-Tyr supplement from MTyr–OANPs activates melanogenesis by increasing tyrosinase activity and promoting melanosome synthesis, which significantly impacts glycolysis inhibition and consequently induces cell death. 3. Since melanin is a natural photothermal agent, combining MTyr–OANPs with photothermal therapy can completely eradicate B16F10 melanoma in C57BL/6 mice.

Melanin metabolism is an intricate process that involves the coordination of environmental physical cues, endogenous signaling pathways, and compartmentalized intracellular metabolism[4]. Metabolic dysregulation can lead to pigmentary disorders and alter susceptibility to cutaneous carcinogenesis. In this work, in stark contrast to other melanogenesis-promoting stimuli such as ultraviolet radiation, which might induce tumor metastasis, MTyr–OANPs inhibited the growth and cell migration of melanoma cells, rather than facilitating tumor metastasis[3]. Notably, certain components of the tumor microenvironment (TME), including immune cells (*e.g.*, $CD8^+$T cells, tumor-associated macrophages, regulatory T cells) and stromal cells (*e.g.*, cancer-associated fibroblasts and endothelial cells), undergo significant metabolic rewiring to regulate tumor progression[5]. Specifically, the tumor-intrinsic glycolysis pathway confers resistance to T cell-mediated killing and contributes to immune evasion[6]. Targeting this pathway can sensitize T cell-mediated killing of tumor cells, thereby potentiating anti-tumor immunity[7]. Additionally, photothermal therapy can enhance immune cell infiltration in tumors, rewire pathways in the TME towards a pro-inflammatory state, and improve the tumoricidal effect, especially when combined with immunotherapy[8,9]. Therefore, further investigation into the metabolic regulation of TME components by MTyr–OANPs is crucial for understanding its subsequent impact on the immune microenvironment within tumor tissues.

Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2024.07.015

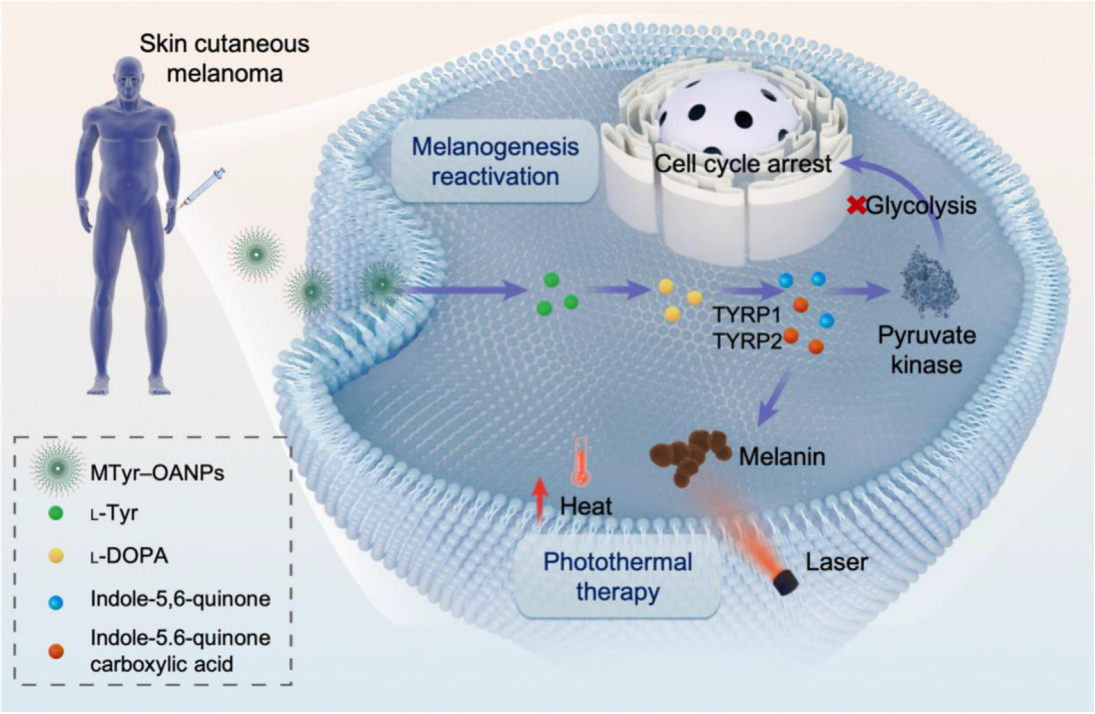

Figure 1 L-Tyrosine-oleylamine nanomicelles (MTyr−OANPs) for metabolism reactivation therapy.

Although some progress has been made in tumor metabolic therapy, significant challenges remain, including adverse effects, metabolic heterogeneity and adaptability, and the complex interactions between tumor cells and TME components[10]. On the one hand, identifying more desirable metabolic targets by employing spatial and single-cell multi-omics technologies together with computational methods holds tremendous potential and warrants further investigation. On the other hand, inspired by this work[3], we should explore changes in relevant metabolites during metabolic therapy to understand the biological function and dynamics of molecular networks. Building upon this, rational combinations with chemotherapy, radiotherapy, phototherapy, immunotherapy, and other therapeutic modalities should be considered. Of note, it is essential to meticulously determine the optimal combination treatment regimens, whether to use a simultaneous approach or a sequential strategy. Furthermore, it is important to explore the effectiveness and metabolic plasticity of synergistic interactions with other therapeutic modalities across various cancer types, stages of tumor progression, and treatment phases. Exciting opportunities lie ahead for targeting cancer metabolism therapeutically, which will likely contribute to the advancement of personalized medicine for refractory diseases associated with metabolic disorders.

Author contributions

Xi Hu: Writing − review & editing, Writing − original draft. Daishun Ling: Writing − review & editing, Conceptualization.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Received 14 June 2024
Received in revised form 13 July 2024
Accepted 14 July 2024