

Disulfidptosis Nanoinducer Interrupts Tumor Metabolic Privilege to Boost Sustained Immunotherapy

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ABSTRACT: Malignant tumor metabolic reprogramming drives proliferation and immune evasion by hijacking essential nutrients and shaping an immunosuppressive microenvironment. Although targeting tumor metabolism offers therapeutic promise, selectively modulating aberrant metabolic pathways without affecting normal cells remains a major challenge. Disulfidptosis, a recently identified form of metabolism-dependent regulated cell death, may offer an avenue for metabolic disruption; however, its immunomodulatory potential remains unexplored. Here, a disulfidptosis nanoinducer (CYBC NPs), which was constructed with cancer cell membrane-camouflaged nanoplateform coloaded with cystine and the GLUT1 inhibitor BAY-876, was designed to selectively induce disulfidptosis in triple-negative breast cancer cells. By concurrently blocking glucose uptake and supplementing cystine, CYBC NPs triggered disulfidptosis-mediated cytoskeletal collapse, relocated tumor metabolic fluxes, and induced immunogenic cell death. This metabolic perturbation promoted dendritic cell maturation, M1-like macrophage polarization, and cytotoxic T lymphocyte activation, thereby reversing ITME and suppressing tumor growth. Notably, CYBC NPs elicited robust, nonexhausted antitumor immunity and generated durable immune memory, effectively preventing tumor recurrence and metastasis. Together, our study demonstrated the implementation of disulfidptosis as a standalone immunotherapeutic strategy, offering a paradigm shift in metabolism-driven cancer immunotherapy.

KEYWORDS: disulfidptosis, metabolic regulation, immunosuppressive tumor microenvironment, T cell exhaustion, immune memory

INTRODUCTION

Emerging evidence reveals that metabolic dysregulation in tumors not only maintains their malignant phenotype but also underlies the formation of an immunosuppressive tumor microenvironment (ITME), thereby impeding the development of effective antitumor immunity.^{1,2} At the core of this metabolic-immune interplay lies intense nutrient competition between cancer cells and immune cells. Tumor cells exhibit an excessive uptake of key metabolites (e.g., glucose, lipid, and amino acids) through upregulated transporters and nutrient-sensing signaling pathways.³ This metabolic competition impairs the functionality of effector immune cells, notably, CD8⁺ T cells and natural killer (NK) cells, which rely on these essential substrates to sustain activation and proliferation. Concurrently, the accumulation of immunosuppressive metabolites (e.g., lactate, kynurenine, and adenosine) contributes to the reprogramming of tumor-associated macrophages (TAMs) toward an M2-like,⁴ tumor-promoting phenotype, the

expansion of myeloid-derived suppressor cells (MDSCs),⁵ and the upregulation of inhibitory immune checkpoints, such as PD-1 and PD-L1.⁶ Collectively, these events orchestrate a multilayered immunosuppressive network, particularly pronounced in immunologically “cold” tumors, contributing to poor responses to current immunotherapies.⁷

Given these findings, targeting tumor-intrinsic metabolic vulnerabilities has emerged as a promising approach to overcome immune resistance.^{8,9} However, most metabolic interventions predominantly focus on individual pathways (e.g., glycolysis,¹⁰ lipid synthesis,^{11,12} or amino acid metabo-

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