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Metabolic plasticity: Metabolic targeted drug classes, delivery systems, and combination therapies for cancer treatment

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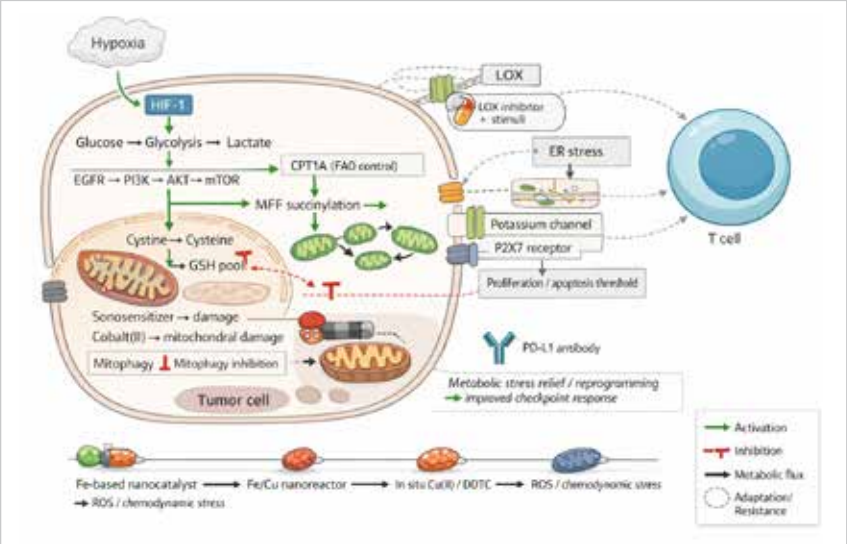

Mechanism of Metabolic Stress Reprogramming to Enhance Immune Checkpoint Therapy.

Under hypoxic conditions, tumor cells activate HIF-1, driving a shift in glucose metabolism from glycolysis to lactate production, and linking EGFR/PI3K/AKT/mTOR signaling to maintain metabolic adaptation. Simultaneously, cysteine is replenished through cystine uptake and reduction, expanding intracellular GSH reserves to buffer

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oxidative stress. CPT1A, a key regulator of fatty acid oxidation, and its downstream MFF succinylation participate in mitochondrial dynamics regulation. In the therapeutic module, Fe-based nanocatalysts assemble into Fe/Cu nanoreactors in the tumor microenvironment and generate Cu (II)/DDTC in situ, inducing ROS-mediated chemokinetic stress; combined with a sonosensitive agent/Co (II), this induces mitochondrial damage and inhibits mitophagy, further exacerbating metabolic stress. Metabolic and organelle stress can affect tumor-T cell interactions through the LOX-related axis and ER stress, and regulate potassium channels and P2X7 receptor signaling, thereby altering T cell proliferation/apoptosis thresholds; combined with PD-L1 antibodies, metabolic stress relief/reprogramming can be achieved, enhancing immune checkpoint therapy responses.

Abstract

Cancer metabolism has evolved from a descriptive feature to a therapeutic target integrating oncogenic signaling, tissue constraints, and immune regulation. Metabolic reprogramming can meet biosynthetic demands under fluctuating nutrition and oxygen, maintain redox homeostasis while preserving mitochondrial function, and shape an immunosuppressive tumor microenvironment through metabolite gradients, acidity, and substrate competition. This review summarizes the major metabolic modules that sustain malignant progression, including: glucose utilization and its lactate-driven ecosystem effects; lipid metabolic remodeling that couples fatty acid oxidation to mitochondrial dynamics and translocation behavior; amino acid-dependent enhancements of thiol buffering and ferroptosis resistance; and mitochondrial energy programs that enable adaptive switching under therapeutic stress. Emerging metabolic-targeted therapies are categorized, encompassing inhibition of nutrient signaling pathways and hypoxia adaptation, lipid and amino acid-directed interventions that disrupt buffering circuits, and strategies that inhibit mitochondrial quality control. A recurring theme is that therapeutic efficacy is often limited by metabolic plasticity, which is enhanced by autophagy, stress response signaling, and synergistic adaptations among the tumor, matrix, and immune system. Therefore, delivery innovation has become a mechanistic determinant, as antibody-drug conjugates, prodrug structures, catalytic nanoreactors, and biomimetic carriers can localize metabolic stress, amplify reaction chemistry, and promote the co-localization of co-perturbations. Finally, rational combination regimens with chemotherapy, targeted therapy, and immunotherapy are discussed, aiming to prevent compensatory reprogramming while transforming the metabolically inhibited microenvironment into an immune-allowed state.

KEYWORDS

Cancer metabolic reprogramming, Metabolic targeted drugs, Metabolic therapy, Tumor microenvironment

Introduction

Cancer metabolism has matured from a descriptive phenotype into a tractable therapeutic axis, because metabolic wiring sits at the convergence of oncogenic signaling, tissue context, and immune control(1). Contemporary work frames metabolic reprogramming as a dynamic solution to three coupled pressures: (i) sustaining biosynthetic throughput under fluctuating nutrient and oxygen supply, (ii) buffering redox stress while preserving mitochondrial competence, and (iii) shaping a tumor microenvironment (TME) that suppresses antitumor immunity. These pressures produce non-uniform metabolic states across patients, tumor regions, and cellular compartments, including cancer cells, stromal cells, and immune infiltrates(2, 3). Such heterogeneity helps explain why "one-pathway" metabolic inhibition frequently yields transient responses, yet also reveals selective liabilities when a tumor

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becomes locked into a nutrient dependency, a redox bottleneck, or a mitochondrial program required for survival. Parallel perspectives that focus on the immune landscape argue that metabolism is not merely a tumor-intrinsic trait; rather, metabolite gradients, acidity, lipid availability, and competition for key substrates govern immune activation, differentiation, and exhaustion, making immunometabolism a central determinant of treatment response(4, 5).

A second, equally consequential inflection point is the rise of therapeutic modalities that can operationalize metabolic concepts. Small molecules targeting enzymes or transporters remain foundational, yet the field now includes antibody–drug conjugates (ADCs) with improved intracellular trafficking properties(6, 7), catalytic nanoreactors that amplify oxidative chemistry in situ(8, 9), prodrug architectures that "gate" bioactivation to the TME(10, 11), and biomimetic carriers engineered for organ- or cell-type tropism(12). Importantly, these delivery innovations do not simply improve pharmacokinetics; they can re-shape the effective mechanism by restricting exposure, concentrating reactive intermediates, or forcing co-localization of otherwise incompatible therapies. Work spanning smart liposomal systems for brain malignancies (13), microenvironment-responsive nanoparticle platforms in breast cancer(14), and nanomaterials designed to interface with antitumor immunity suggests that metabolism-targeted therapy is increasingly a problem of systems engineering: selecting the right vulnerability, delivering the perturbation to the right compartment, then preventing compensatory rewiring. This Review synthesizes mechanistic themes across major metabolic modules—glucose metabolism, lipid metabolism, amino-acid dependencies, and mitochondrial energetics—while evaluating how emerging drug classes and delivery strategies can overcome resistance and unlock combination regimens with chemotherapy, targeted therapy, and immunotherapy(15, 16).
epigenetics in the TME, and outlines translational strategies grounded primarily in your curated evidence base.

Metabolic reprogramming in cancer

Glucose metabolism reprogramming

Enhanced glucose uptake and glycolytic flux remain archetypal tumor traits, yet recent evidence emphasizes context-specific drivers and downstream ecosystem effects. In lung adenocarcinoma, decreased expression of surfactant protein C (SFTPC) has been associated with heightened glycolysis and increased proliferative capacity, consistent with a model in which lineage features intersect with carbon metabolism to support growth(17). Hypoxia responses further reinforce glycolysis, partly through hypoxia-inducible factor-1 (HIF-1), whose role in prostate cancer has been highlighted as a therapeutically actionable integrator of glucose metabolism, angiogenesis, and survival signaling(18). Lactate produced by glycolysis is increasingly viewed as an information-rich metabolite rather than a passive waste product: it acidifies extracellular space, reshapes antigen presentation and effector function, and fuels metabolic symbiosis through monocarboxylate transport. Immunometabolic frameworks propose that lactate and acidity blunt T-cell activity and promote immune suppression in the TME, thus positioning lactate generation or transport as a lever to convert immune "cold" niches into more permissive environments for immune attack(5). These concepts are also informing translational tools for monitoring disease: a glucometer-based strategy that links glucose consumption to the detection of circulating tumor cells (CTCs) suggests that metabolic activity can be exploited for low-resource diagnostics, potentially enabling frequent sampling in lung cancer settings where real-time monitoring is clinically valuable(19). Mechanistically, the key point is not that glycolysis is uniformly "high," but that tumors often configure glucose handling to satisfy redox buffering, nucleotide synthesis, and adaptation to hypoxia—features that create actionable dependencies on transporters, rate-limiting enzymes, or lactate exchange, especially when paired with therapies that stress DNA repair, redox homeostasis, or immune function(5, 20).

Lipid metabolism abnormalities

Lipid metabolism provides both building blocks and signaling capacity, supporting membrane synthesis, post-translational modifications, and bioenergetic plasticity. A representative mechanistic advance is the demonstration that carnitine

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palmitoyltransferase 1A (CPT1A)—a gatekeeper of mitochondrial fatty-acid import—can promote mitochondrial fission through MFF succinylation in ovarian cancer, linking fatty-acid oxidation (FAO) to mitochondrial dynamics and, by extension, to survival programs that may enable dissemination or therapy resistance(21). In breast cancer, metastatic competency has been tied to microenvironmental lipids and niche-dependent metabolic constraints; dietary or systemic interventions have been discussed as means to modulate the liver metastatic niche, underscoring that lipid availability is not only cell intrinsic but also organismal(22). Beyond FAO, lipid signaling networks intersect with extracellular matrix remodeling and invasion. A mechanochemically synergistic strategy combining a lysyl oxidase (LOX) inhibitor with a stimuli-responsive drug platform in breast cancer emphasizes how metabolic or enzymatic remodeling of the microenvironment (e.g. collagen cross-linking) can cooperate with drug delivery logic to disrupt metastatic progression(23). Lipid pathways also cross-talk with membrane receptors and ion channels, affecting signaling thresholds that regulate metabolism itself; for example, the P2X7 receptor has been described as a critical regulator and target in breast cancer, potentially influencing both intracellular bioenergetics and inflammatory microenvironment cues(24). Collectively, these findings support a modern view in which lipid metabolism is a multi-scale system: mitochondrial FAO and dynamics (tumor cell survival), stromal remodeling (invasion), and receptor-coupled signaling (immune and stress pathways) co-determine vulnerability. Consequently, lipid-targeted therapy must anticipate rapid switching between synthesis and oxidation, as well as compensatory uptake from the microenvironment, making combination strategies and compartment-specific delivery increasingly important(21, 23).

Amino acid metabolism dependence

Amino-acid metabolism supplies carbon and nitrogen for protein and nucleotide synthesis, while also governing redox balance through glutathione and related thiol pathways. Several lines of evidence underscore that amino-acid handling is frequently coupled to oxidative stress responses and regulated cell death programs. In hepatocellular carcinoma (HCC), a small-molecule sulfone compound has been reported to downregulate SLC7A11 (xCT), inducing ferroptosis, thereby highlighting cystine import as a redox choke point that can be therapeutically exploited in liver cancer contexts(25). In osteosarcoma, sulforaphane has been shown to promote ferroptosis through p62-linked autolysosomal degradation of SLC7A11, suggesting that lysosome–autophagy circuitry can be harnessed to disable cystine uptake and destabilize redox homeostasis(26). Importantly, these ferroptosis-adjacent vulnerabilities are not limited to direct transporter inhibition; they can be amplified through materials that perturb thiol buffering. A trimethyl chitosan–cysteine nanoparticle system developed for HCC illustrates how thiol chemistry and delivery vehicles can be coupled to influence tumor redox states and therapeutic response(27). Folate metabolism provides another clinically relevant dimension, because folate status modulates one-carbon flux and can shape chemotherapy-associated toxicity; a dedicated synthesis of folate–chemotherapy interactions highlights that host metabolism is a determinant of tolerability, which in turn influences dose intensity and combination feasibility(28). Taken together, these studies support a broader conceptual shift: amino-acid metabolism is often best understood as a set of "buffering circuits" (thiols, one-carbon units, nitrogen handling) that stabilize tumor growth under stress. Therapies that collapse buffering capacity—especially when paired with ROS-generating modalities or DNA-damaging treatments—may induce disproportionate tumor injury, provided that delivery and patient selection strategies mitigate systemic toxicity(26, 29).

Mitochondrial metabolism and oxidative phosphorylation (OXPHOS)

Mitochondria are no longer framed as passive ATP factories in cancer; instead, they are hubs for redox control, apoptotic priming, biosynthetic precursor generation, and signaling. One consequence is the emergence of OXPHOS-dependent subpopulations that can survive glycolytic stress, metastatic bottlenecks, or therapy exposure. Mechanistically, mitochondrial dynamics appear central to this adaptation: CPT1A-driven FAO can promote fission and likely re-distribute metabolic capacity across daughter mitochondria, enabling survival under fluctuating nutrient conditions(30). Therapeutically, several platforms aim to force mitochondrial failure or disable mitochondrial quality control. A biomimetic nanovesicle strategy integrates a mitochondria-synthesized sonosensitizer with mitophagy inhibition, thereby increasing mitochondrial damage persistence and strengthening tumor killing—an approach that explicitly targets the "repair capacity" of mitochondrial networks rather than only initial injury(31). A cobalt (II) agent reported to induce mitochondrial damage has been positioned as a low-toxicity strategy that

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can couple chemotherapy-like cytotoxicity with immunotherapy-relevant immune activation, suggesting that mitochondrial injury can serve as a bridge between direct tumor killing and immune engagement(32). Stress adaptation also intersects with autophagy and energy metabolism in resistant disease: a CLTC–VMP1 fusion in osteosarcoma has been linked to autophagy activation and altered energy metabolism in cisplatin-resistant settings, reinforcing the idea that mitochondrial and autophagic programs can cooperate to buffer therapy stress(33). The practical implication is that mitochondrial targeting must be contextualized: some tumors remain glycolysis-dominant, yet rely on mitochondria for redox balance; others transition toward OXPHOS under drug pressure. Effective therapy therefore requires either (i) stratification of mitochondrial dependence or (ii) combination regimens that block switching routes such as autophagy, FAO, or stress response signaling(31, 33).

Classification of metabolism-targeted anticancer drugs

Drugs targeting glucose metabolism

Therapeutic targeting of glucose metabolism spans direct enzyme inhibition, transporter blockade, and disruption of upstream nutrient signaling or hypoxia adaptation. An illustrative example is an ethyl difluoro coumarin acetate reported to attenuate malignant behavior in non-small cell lung cancer (NSCLC) via EGFR/PI3K/AKT/mTOR signaling, emphasizing that pathway-level inhibition can re-shape metabolic state while also suppressing proliferation and survival signaling(34). Complementary reviews of PI3K/AKT/mTOR modulation by flavonoids underscore that "metabolic targeting" can be achieved through pleiotropic regulators that suppress anabolic signaling, alter nutrient sensing, and modulate stress pathways; such agents may be most useful when positioned as adjuvants that reduce pathway activity and sensitize tumors to more direct metabolic or cytotoxic insults(35). Hypoxia signaling forms a parallel layer: HIF-1 has been highlighted as a target in prostate cancer because it couples oxygen availability to glycolytic rewiring, angiogenic output, and treatment resistance features, making it an attractive node for multi-phenotype suppression(18). These pathway-level approaches are increasingly complemented by delivery systems that restrict exposure and increase intratumoral potency. For instance, microenvironment-responsive nanoparticle designs for breast cancer have been catalogued as a means to exploit endogenous triggers (pH, redox, enzymes) to increase drug activity specifically in malignant tissue(14). In brain tumors, smart liposomal systems aim to solve both pharmacologic (BBB penetration) and biologic (heterogeneity, hypoxia) constraints, enabling metabolic or signaling drugs to reach relevant compartments(13). Finally, metabolic state can be leveraged diagnostically: a glucometer readout for detecting CTCs illustrates that glucose utilization itself can be co-opted for signal generation, potentially offering a practical bridge between metabolic biology and clinical monitoring. Overall, glycolysis-adjacent targeting is best viewed as an ecosystem intervention: the goal is not solely to lower glycolytic flux, but to disrupt coupled outputs—lactate accumulation, acidity, anabolic signaling—while using delivery strategies to minimize systemic liabilities(5, 35).

Drugs targeting lipid metabolism

Lipid metabolism offers diverse intervention points: FAO control, lipid synthesis inhibition, cholesterol/mevalonate modulation, and suppression of lipid-driven signaling that supports metastasis or immune evasion. Mechanistic work linking CPT1A to mitochondrial fission via MFF succinylation illustrates why FAO is not merely a fuel choice; it can be embedded in organelle remodeling programs that influence cell fate under stress(30). In prostate cancer, palmitic acid has been reported to inhibit tumor growth through PI3K/Akt signaling, illustrating that lipid species can also act as signaling modulators that intersect with nutrient pathways. While palmitate biology in cancer is context dependent, this study highlights a broader principle: lipid availability and lipid signaling can become exploitable variables, particularly when tumors show defined dependencies on PI3K/Akt-driven anabolism or membrane receptor activity(36). Remodeling of

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extracellular matrix and microenvironment provides another entry point. A combined strategy using a LOX inhibitor with a stimuli-responsive platform in breast cancer indicates that targeting microenvironmental enzyme activity can synergize with drug delivery logic to limit invasion and metastasis, potentially reducing the adaptive space available for metabolic escape(23). Membrane receptors and ion channels provide additional control knobs; potassium channels have been discussed as promising anticancer targets, with implications for proliferation control, apoptosis thresholds, and possibly metabolic regulation through membrane potential and ion homeostasis(37). The P2X7 receptor likewise has been positioned as an actionable regulator in breast cancer, and its immunologic roles raise the possibility that targeting purinergic signaling might simultaneously alter tumor bioenergetics and inflammatory cues(24). Therapeutic modalities in this space increasingly rely on advanced delivery architectures, including in situ gelling nanogels for localized breast cancer therapy and targeted micelle systems for controlled delivery of cytotoxics(38, 39). The key lesson is that lipid metabolism–targeted therapy rarely succeeds as a single enzyme story; efficacy often depends on how lipid flux, organelle state, and membrane signaling are co-regulated, which in turn favors combination regimens or multifunctional platforms that address both tumor-intrinsic metabolism and microenvironmental adaptation(37, 39).

Drugs targeting amino acid metabolism

Amino-acid targeting strategies frequently converge on redox control, because cystine/cysteine handling, glutathione synthesis, and lipid peroxidation buffering create a narrow corridor for survival in oxidative environments. Two studies exemplify this vulnerability through SLC7A11 inhibition or degradation: in HCC, downregulation of SLC7A11 by a small-molecule sulfone has been associated with ferroptosis induction, whereas in osteosarcoma, sulforaphane has been reported to promote autolysosomal degradation of SLC7A11 via p62, again leading to ferroptosis. These findings suggest that cystine import is a shared vulnerability across distinct tumor types, while the upstream mechanism—direct inhibition versus autophagy-mediated degradation—can vary, which may matter for resistance and combination design(25, 26). Materials-based strategies aim to amplify oxidative stress or disable buffering in a spatially restricted way. A calcium phosphate–mineralized nanoplatform designed for triple-negative breast cancer (TNBC) emphasizes multi-pathway targeting and includes ferroptosis-relevant logic, consistent with the idea that ferroptosis may be most potent when combined with additional metabolic or stress perturbations that prevent compensatory antioxidant responses(29). In HCC, a trimethyl chitosan–cysteine nanoparticle system underscores how thiol chemistry can be integrated with delivery to alter redox handling and therapeutic effect(27). In gastric cancer, biomimetic nanoparticles incorporating polyphyllin B have been reported to synergize with glutathione-triggered release logic, supporting a design principle in which tumor-elevated thiols become the activator of a redox-disruptive payload(40). Beyond tumor killing, amino-acid metabolism also intersects with host toxicity and immune competence. Folate metabolism has been synthesized as a determinant of chemotherapy-associated toxicity; this line of work is practically important because metabolic adjuncts that improve tolerability can expand the feasible dose window for metabolic combinations or oxidative therapies(41). Overall, amino-acid targeting is increasingly defined by “buffer collapse” strategies—forcing tumors to cross a redox threshold—while using tumor-selective activation or delivery to reduce systemic liabilities.

Drugs targeting mitochondria and energy metabolism

Mitochondrial targeting strategies span direct injury, inhibition of mitochondrial bioenergetics, and disruption of mitochondrial quality control. A biomimetic nanovesicle platform that combines a mitochondria-synthesized sonosensitizer with mitophagy inhibition exemplifies a dual-hit design: it increases mitochondrial damage generation, then prevents mitochondrial repair, thereby converting reversible stress into lethal injury. A cobalt (II) agent reported to trigger mitochondrial damage illustrates a chemically distinct route to impair mitochondrial viability, with the notable framing that mitochondrial damage can couple cytotoxicity to immunotherapy-relevant mechanisms, possibly via immunogenic cell death or altered inflammatory signaling(32). The importance of mitochondrial quality control is reinforced by resistant disease biology: the CLTC–VMP1 fusion in cisplatin-resistant osteosarcoma has been linked to autophagy activation and energy metabolism changes, suggesting that autophagy can act as a survival valve when mitochondrial or metabolic stress accumulates under treatment(33). That view is consistent with broader discussions of endoplasmic

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reticulum (ER) stress in osteosarcoma, where unfolded protein response programs interface with metabolism and survival, potentially providing additional co-targets to prevent adaptation(42). In pancreatic cancer, activation of DDIT3 (CHOP) by dehydroevodiamine has been reported to inhibit tumor growth and stemness, hinting that stress-response manipulation can suppress malignant programs that are often metabolically supported(43). Translationally, mitochondria-centered strategies also motivate tumor models that preserve metabolic phenotype. Integrated characterization of hepatobiliary tumor organoids has been used to map pharmacogenomic interactions, providing a platform where mitochondrial state, nutrient dependence, and drug response can be examined in a patient-relevant context(44). In sum, mitochondrial targeting is increasingly "systems-based": success depends on disabling mitochondrial injury repair (mitophagy, autophagy, stress responses) while selecting contexts where mitochondrial dependence is high or where therapy pressure forces a shift toward mitochondrial programs.

Nanomedicine-targeted metabolic reprogramming

A unifying thread across multiple tumor types is that delivery strategy can become the metabolic intervention. Chemodynamic and catalytic approaches exemplify this principle by amplifying oxidative chemistry inside tumors, thereby overwhelming redox buffering. Macrophage-mimic hollow mesoporous Fe-based nanocatalysts have been reported to enable self-amplified chemodynamic therapy, leveraging tumor-localized catalysis to generate cytotoxic stress(45). Porous Fe/Cu nanoreactors provide a related "dual insurance" design for precision chemotherapy plus chemodynamic therapy, implying that catalytic ROS generation can synergize with conventional drugs by increasing damage load while constraining systemic exposure(9). Copper (II)/diethyldithiocarbamate generated within hollow mesoporous silica similarly frames the tumor as a reaction vessel, enabling in situ formation of active species for therapy(8). Prodrug architectures expand this logic to controlled assembly and release: redox-sensitive carrier-free nanoparticles formed from paclitaxel–tetramethylpyrazine conjugates illustrate how self-assembly can be coupled to TME redox triggers, enabling combination chemotherapy within a single chemical scaffold(10). Sequential self-assembly and release of a camptothecin prodrug further suggests that temporal control over activation can improve tumor targeting and reduce off-target burden(11). ADCs provide another modality axis: a folate receptor-α (FRα)-targeted TOP1 inhibitor–loaded ADC, as well as strategies that modulate HER2 internalization to enhance antibody–drug potency, highlight that intracellular trafficking and payload release can govern effective metabolic stress and cytotoxicity(46). Immune-facing biomimicry adds a further layer, exemplified by brain-targeting biomimetic nanoparticles delivering celastrol plus LY2157299 to reverse glioma immunosuppression, as well as a minimalist multifunctional nano-prodrug designed to reverse drug resistance and integrate with PD-L1 antibody therapy in HCC(12). Across these platforms, the main insight is that nanomedicine can operationalize metabolic targeting by concentrating stress, co-delivering synergistic perturbations, and engaging immune compartments that are otherwise metabolically suppressed.

Drug resistance and metabolic plasticity

Resistance to metabolism-targeted therapy frequently arises not from a single mutation, but from network-level rewiring that restores biomass production, redox buffering, or energy supply through alternative routes. Multiple studies illustrate how stress adaptation and organelle quality control serve as central resistance valves. In cisplatin-resistant osteosarcoma, a CLTC–VMP1 fusion has been linked to autophagy activation and altered energy metabolism, suggesting that enhanced recycling capacity can buffer both nutrient stress and drug-induced damage(33). ER stress programs, discussed in osteosarcoma more broadly, provide additional adaptive capacity by reprogramming translation, lipid synthesis, and antioxidant responses; such programs may stabilize survival under metabolic inhibition and create opportunities for

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rational co-targeting(47). Drug resistance is also shaped by metabolic heterogeneity within tumors, where subclones can switch between glycolysis and mitochondrial respiration, or between endogenous lipid synthesis and lipid scavenging, depending on microenvironmental constraints. PDAC-focused syntheses emphasize that physical structure—hypovascularity, dense stroma—restricts nutrient delivery, thereby selecting for tumors with strong metabolic flexibility and enhanced scavenging pathways(48). In this context, pathway inhibitors that suppress EGFR/PI3K/AKT/mTOR signaling can reduce anabolic drive, yet tumors may compensate through autophagy, alternative receptor signaling, or mitochondrial re-optimization, leading to incomplete responses when used alone.

A major pragmatic challenge is that plasticity is not solely tumor intrinsic; stromal and immune compartments co-evolve under therapy, producing metabolite gradients that can either suppress immune killing or provide alternative fuels to resistant clones(49). Macrophages have been framed as "traffic centers" of the immune microenvironment, consistent with the idea that myeloid states modulate nutrient availability, inflammatory cues, and drug response(50). Functional subtype analyses in angioimmunoblastic T-cell lymphoma (AITL) that integrate immune infiltration with drug specificity further highlight that response determinants can include immune composition and functional state, which are metabolically coupled even in hematologic malignancies(51). Translational models capable of preserving multi-cellular architecture and metabolic phenotype are therefore essential. Hepatobiliary tumor organoids characterized for pharmacogenomic interactions provide one such platform to investigate drug response landscapes while retaining aspects of tumor identity and potentially relevant metabolic programs(44, 52). Complementary approaches using plasma proteomics with Mendelian randomization to prioritize therapeutic targets offer a population-level route to identify causal nodes that may govern disease biology, including metabolism-adjacent proteins or pathways(53, 54). Together, these studies suggest a resistance-aware strategy: define the dominant buffering circuit (autophagy, mitochondrial repair, redox control), select delivery logic that forces tumor-localized stress, then design combinations that prevent adaptive switching across metabolic states.

Combination strategies involving metabolism-targeted drugs

Combination regimens are increasingly the practical route to durable benefit, because they can exploit metabolic dependencies while blocking escape routes. One rationale is that many standard therapies impose metabolic stress indirectly. Chemotherapy and radiotherapy generate DNA damage and ROS, increasing demand for nucleotide synthesis, NAD(P)H regeneration, and glutathione buffering(55). Metabolism-targeted agents that reduce antioxidant capacity or impair repair-adjacent metabolism can therefore amplify cytotoxicity. A chitosan-based nanoparticle system co-delivering docetaxel and curcumin has been reported to improve chemoimmunotherapy in lung cancer, illustrating a design where cytotoxic chemotherapy is paired with a bioactive compound that can modulate stress and immune responses, with the carrier enabling coordinated delivery(16). In TNBC, a multifunctional nanoparticle strategy targeting metabolic reprogramming alongside DNA damage response has been reported in drug-resistant settings, reflecting a logic that couples metabolic inhibition to impaired repair capacity, thereby raising the effective damage burden beyond the cell's buffering range(56). Combination thinking also extends to targeted therapy pairings. A biotin-guided Pt (IV) amphiphilic prodrug has been reported to synergize with CDK4/6 inhibition, suggesting that coupling cell-cycle constraint with mitochondrial/chemical stress can enhance efficacy while potentially reducing the required intensity of either component(57). In breast cancer, LOX inhibition combined with stimuli-responsive delivery emphasizes that microenvironment remodeling can sensitize tumors to drug effects, likely by limiting invasion routes and altering stromal support for metabolic adaptation(58). Host metabolism is also relevant: work synthesizing folate's role in chemotherapy-associated toxicity underscores that metabolic adjuncts may enable higher-intensity regimens or broaden the

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feasible combination space by improving tolerability.

Immunotherapy combinations represent a particularly compelling frontier, because metabolic stress is deeply intertwined with immune competence in the TME. Reviews focusing on metabolic alterations that restrain antitumor immunity propose that reversing nutrient competition, acidity, and lipid stress can improve checkpoint efficacy(59). Several platforms explicitly integrate immune-facing goals. A minimalist multifunctional nano-prodrug has been designed to reverse drug resistance and interface with PD-L1 antibody therapy in HCC, reflecting an intent to couple tumor killing with immune checkpoint response. Brain-targeting biomimetic nanoparticles co-delivering celastrol and LY2157299 have been reported to reverse glioma immunosuppression, suggesting that metabolic or signaling perturbations can be targeted to immune-relevant niches in the central nervous system(12). A cobalt (II) agent has been framed as a low-toxicity approach that induces mitochondrial damage while supporting combined chemotherapy and immunotherapy effects, aligning with the concept that mitochondrial injury can generate immune-stimulatory signals or alter suppressive programs. Reviews of nanomaterials in tumor immunotherapy further emphasize that the delivery vehicle can be tuned to target immune cells, reprogram macrophages, or enhance antigen presentation, thereby altering the metabolic rules of engagement in the TME(60). Clinically, glutaminase inhibition with telaglenastat has advanced into early trials, and broader immunometabolism literature supports combining metabolic drugs with checkpoint blockade when metabolic suppression constrains T cell activity(61, 62). Collectively, combination strategy design should prioritize: (i) identifying the dominant metabolic bottleneck, (ii) selecting partners that create orthogonal stress (DNA damage, immune activation), and (iii) using delivery systems that enforce co-localization and reduce systemic toxicity.

Conclusion

Metabolism-targeted therapy has shifted from a singular emphasis on glycolysis inhibition to a multi-compartment strategy that integrates tumor-intrinsic dependencies, microenvironmental constraints, and immune function. Across glucose, lipid, amino-acid, and mitochondrial modules, a recurring theme is that tumors survive by maintaining buffering capacity—redox balance, organelle quality control, stress-response signaling—rather than by maximizing any single pathway. This framing helps reconcile apparent contradictions in the literature: glycolysis can dominate in one context, yet mitochondrial programs become essential under therapy pressure; FAO can fuel growth, yet mitochondrial dynamics and signaling effects may be the deeper liability; cystine import may be dispensable under low stress, yet becomes a critical bottleneck when ROS or lipid peroxidation rises. Therapeutic success therefore depends on forcing tumors into metabolic corners while preventing compensatory rewiring.

For translational researchers, three take-home messages emerge. First, patient selection must consider metabolic state, microenvironmental context, and immune composition, because response determinants are often network-based rather than gene-based. Second, delivery logic is increasingly inseparable from mechanism: catalytic nanoreactors, sequential prodrugs, ADC trafficking control, and biomimetic targeting can convert theoretical vulnerabilities into actionable, tumor-restricted perturbations. Third, durable efficacy will likely come from rational combinations that pair metabolic collapse (e.g. redox buffer disruption, mitochondrial injury, nutrient signaling suppression) with orthogonal stressors such as DNA damage or immune activation, while co-targeting adaptive valves like autophagy or stress response programs. As these principles are operationalized in physiologic tumor models and early clinical studies, metabolism-targeted therapy is poised to function as a central hub connecting tumor biology with treatment strategy, rather than as a niche add-on to existing regimens

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