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Metabolic Recovery after Anticancer Treatment Withdrawal: An Integrative Review of Enzyme Regulation, Proteome Remodeling, and Nutrient Dependencies in Persistent Tumor Cell States

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Abstract

Persistent tumor cells that survive anticancer therapy can remain viable despite profound suppression of proliferation, yet survival during treatment and recovery after treatment withdrawal are biologically distinct events. This integrative review examines how metabolic state, enzyme regulation, proteome remodeling, nutrient use, and redox control may shape the transition from treatment persistence to renewed proliferative capacity. Evidence published from 2017 through 2026 was synthesized across experimental, multi-omic, metabolic, lineage-tracing, patient-derived, and review studies, with explicit separation of observations obtained during active treatment from those addressing withdrawal, regrowth, or recurrence. The evidence does not support a single metabolic program shared by all persistent tumor cells. Instead, oxidative phosphorylation, fatty-acid oxidation, lipid-peroxide defense, transsulfuration, lipid synthesis, mitophagy, purine signaling, and one-carbon-linked chromatin regulation recur in different combinations according to tumor lineage and treatment context. These observations indicate that metabolic recovery is best understood as a conditional transition requiring compatibility among pre-existing or treatment-induced cell state, enzyme and proteome organization, redox capacity, and accessible nutrient resources. Therapeutic opportunities therefore lie less in identifying one universal persister metabolism than in defining context-specific recovery dependencies that remain actionable when treatment pressure is removed.

Keywords: Drug-tolerant persister cells, Metabolic recovery, Anticancer treatment withdrawal, Oxidative phosphorylation, Fatty-acid oxidation, Redox homeostasis

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Introduction

Cancer cells that remain viable during otherwise effective therapy can establish drug-tolerant persister states that are phenotypically plastic, frequently reversible, and capable of contributing to later disease recurrence (Russo *et al.*, 2024). Contemporary work increasingly treats these cells as a dynamic reservoir rather than a uniform population, because persistence can arise through different transcriptional, metabolic, epigenetic, and stress-adaptation programs across tumor types and therapeutic exposures (He *et al.*, 2024). This heterogeneity is particularly important for metabolism: a pathway that sustains one persistent state may be dispensable in another, while different upstream programs may converge on similar requirements for ATP production, antioxidant capacity, or membrane-lipid control.

The vulnerability of persister cells to disruption of glutathione peroxidase 4 established lipid-peroxide control as one experimentally tractable feature of selected drug-tolerant states (Hangauer *et al.*, 2017). Related work showed that dependency on lipid-peroxide defense extends to particular therapy-resistant cellular phenotypes, reinforcing the importance of redox state while also demonstrating that the underlying phenotype cannot be reduced to a single treatment history (Viswanathan *et al.*, 2017). These findings helped shift the field from viewing tolerance exclusively through canonical resistance mutations toward examining reversible cellular states that become metabolically vulnerable under continued treatment pressure.

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The origin of those states is itself heterogeneous. Single-cell analyses have demonstrated that rare pre-existing variability and drug-induced reprogramming can both contribute to survival under therapy (Shaffer *et al.*, 2017). Residual melanoma after treatment likewise contains several adaptive cell states rather than one conserved persister identity (Rambow *et al.*, 2018). Consequently, an observed metabolic phenotype after treatment may reflect selection of a pre-existing subpopulation, induction of a new state, or both. This distinction matters because the same measured pathway can have different biological meanings depending on whether it preceded treatment, emerged during adaptation, or becomes necessary only during subsequent recovery.

Persistent cells also vary substantially in proliferative behavior. YAP-dependent transcriptional reprogramming can support treatment-induced tumor dormancy through altered control of apoptosis (Kurppa *et al.*, 2020). Chemotherapy-treated colorectal cancer cells can enter a reversible diapause-like state characterized by broad suppression of growth-associated activity (Rehman *et al.*, 2021), while other models similarly connect suppressed MYC activity with a diapause-like treatment-persistent phenotype (Dhimolea *et al.*, 2021). These observations should not be interpreted as evidence that persistence is synonymous with quiescence. Lineage-resolved experiments have identified cycling persister populations originating from distinct cellular programs, demonstrating that treatment survival can be maintained without a uniform dormant phenotype (Oren *et al.*, 2021).

The central problem is therefore temporal as well as mechanistic. Metabolic properties measured while therapy is present identify how persistent cells survive treatment, but they do not automatically establish what enables those cells to resume growth after treatment is withdrawn. Recovery may require restoration of biosynthetic throughput, mitochondrial competence, redox buffering, nutrient access, signaling permissiveness, or proteome organization that was unnecessary—or differently configured—during the low-proliferation phase. This review consequently distinguishes treatment-associated persistence from post-treatment recovery and examines how enzyme regulation, proteome remodeling, and nutrient dependence may connect the two states without assuming that one universal metabolic trajectory applies across cancers.

Materials and Methods

Integrative Review Design, Evidence Identification, Appraisal, and Synthesis

The review used an integrative design suited to a literature base containing experimental cell models, tumor models, patient-derived systems, lineage-tracing studies, metabolic and multi-omic analyses, and mechanistic reviews. Reporting transparency was informed by relevant PRISMA 2020 principles, particularly clear separation of identification, eligibility, and synthesis decisions, without reclassifying the present work as a systematic review or implying unavailable screening arithmetic (Page *et al.*, 2021). Search reporting was also structured using PRISMA-S principles where applicable, including documentation of search concepts, date limits, source types, and the distinction between reproducible database identification and supplemental citation-based discovery (Rethlefsen *et al.*, 2021).

Eligible evidence addressed malignant-cell persistence, dormancy, drug tolerance, residual disease, or treatment-surviving states and contained information directly relevant to metabolic phenotype, enzyme regulation, proteome or organelle remodeling, nutrient utilization, redox control, withdrawal, regrowth, or recurrence. The evidence window was restricted to 2017–2026. Primary mechanistic evidence was prioritized for biological claims. Recent reviews of pharmacological approaches to persister-cell targeting were used to identify convergent mechanisms and contextualize intervention strategies without substituting secondary synthesis for direct experimental support (Chen, Gowda, *et al.*, 2024). A complementary recent synthesis of drug-induced persister mechanisms was used to assess terminology and breadth of proposed vulnerabilities, while its heterogeneous source base reinforced the decision not to pool outcomes quantitatively (Liu *et al.*, 2025).

Evidence was appraised according to biological-state fidelity, treatment context, temporal design, directness of perturbation, use of rescue or orthogonal validation, metabolic or proteomic resolution, inclusion of patient-derived or in-vivo validation where available, and whether the experiment distinguished treatment survival from post-treatment regrowth. Findings were synthesized qualitatively because tumor lineage, therapeutic exposure, state definition, sampling time, metabolic assay, and outcome measures varied substantially. Mechanistic convergence was recorded only when studies supported the same biological function; similar pathway labels were not assumed to represent equivalent causal mechanisms across models.

The review therefore treated an evidence unit as a biologically interpretable study or experimental report rather than as a citation count. Where exact database retrieval or exclusion totals could not be reconstructed from the executed search environment, those quantities were not inferred.

The methodological structure used to organize the evidence is summarized below.

Table 1 summarizes biological eligibility, evidence-source roles, and appraisal structure used in the integrative review.

Table 1. Biological eligibility, evidence-source roles, and appraisal structure used in the integrative review

Evidence unit or source class	Biological question addressed	Eligible scientific variables	Required contextual information	Primary appraisal emphasis	Role in synthesis
Treatment-persistent	What permits survival during active anticancer treatment?	Metabolic pathway, enzyme activity, redox state,	Tumor lineage, drug exposure, duration,	Direct perturbation, appropriate	Establish on-treatment

tumor-cell experiment		mitochondrial function, nutrient use	persister-state definition	comparator, state fidelity	persistence mechanisms
Withdrawal or regrowth experiment	What permits renewed proliferation after treatment pressure is reduced or removed?	Recovery-associated signaling, metabolic reactivation, organelle state, regrowth competence	Withdrawal timing, residual drug exposure, recovery interval	Explicit temporal design and regrowth endpoint	Separate persistence from recovery
Proteomic or multi-omic study	Which molecular programs accompany or control persistent-state remodeling?	Protein abundance, enzyme-pathway organization, chromatin state, transcriptome, lipidome or metabolome	Biological model and treatment state	Orthogonal validation and causal perturbation	Link regulatory state with metabolic phenotype
Flux or nutrient-dependency study	Which resources are functionally required by persistent or recovering cells?	Carbon source use, fatty-acid oxidation, glutamine utilization, antioxidant metabolism	Medium composition, nutrient availability, treatment state	Tracing, rescue, or functional inhibition	Define resource-dependent vulnerabilities
Patient-derived or organoid evidence	Does a proposed mechanism remain detectable outside conventional cell lines?	State-specific pathway activity or vulnerability	Patient/tumor origin, prior treatment, ex-vivo conditions	Model fidelity and transfer limitations	Strengthen translational relevance
Review or methodological source	How should heterogeneous evidence be classified or reported?	Terminology, evidence categories, reporting standards	Scope and design of secondary source	Methodological appropriateness and duplication control	Contextualization and review governance

Metabolic Characteristics of Persistent Tumor Cells during Anticancer Treatment

Metabolic adaptation during treatment is not dominated by one conserved pathway. In melanoma exposed to BRAF/MEK inhibition, persister-cell survival can depend on ACOX1-mediated fatty-acid oxidation, indicating that lipid catabolism may sustain cells that have entered a treatment-tolerant state (Shen *et al.*, 2020). Other models implicate cholesterol and lipid-handling machinery through NPC1L1, whose inhibition disrupts adaptive responses of chemotherapy-tolerant cells (Zhang *et al.*, 2022). These findings establish lipid metabolism as an important recurrent theme, but they represent different biochemical processes and should not be collapsed into a single "lipid-dependent" persister phenotype.

Mitochondrial remodeling provides a second axis of adaptation. PINK1-mediated mitophagy has been shown to support oxidative phosphorylation and redox homeostasis in drug-tolerant cancer cells, linking organelle quality control with energetic and antioxidant requirements (Li *et al.*, 2023). In EGFR-mutant non-small cell lung cancer, a circular IGF1R transcript was reported to regulate the Parkin–VDAC1 mitophagy axis, with consequences for survival and subsequent regrowth after EGFR-tyrosine kinase inhibitor withdrawal (Wang *et al.*, 2023). The latter finding is especially important because it connects a mitochondrial process measured in the persister state with behavior after treatment removal, while still remaining specific to the tested molecular and therapeutic context.

Persistent cells can also reduce oxidative injury through mechanisms that act downstream of metabolic production. In breast-cancer persisters, P-glycoprotein-mediated removal of toxic lipid-peroxidation products contributes to survival, showing that tolerance can depend on disposal of damaging metabolites rather than solely on reducing their formation (Szebényi *et al.*, 2023). High-grade serous ovarian cancer provides another example of stress-state heterogeneity, in which ATF3 characterizes an aggressive drug-tolerant persister population (Böpple *et al.*, 2024). ATF3 expression alone does not define a metabolic pathway, but its association with an aggressive state illustrates how stress-responsive transcriptional programs can coexist with—and potentially reorganize—metabolic defenses.

Direct metabolic measurements further support context-dependent oxidative metabolism. Endocrine-therapy-tolerant persister cells in estrogen-receptor-positive breast cancer exhibit a vulnerability to oxidative phosphorylation, with quantitative proteomic and metabolic analyses identifying mitochondrial respiration as a functionally important feature of that state (Tau *et al.*, 2025). In BRAF-V600E melanoma, resistance to targeted therapy is instead supported by remodeling of transsulfuration, which strengthens cellular handling of oxidative stress through sulfur-amino-acid metabolism (Borbényi-Galambos *et al.*, 2025). Both settings converge on redox maintenance, yet their upstream substrates, enzymes, and treatment histories differ substantially.

Lipid synthesis can also become functionally important. Therapy-resistant colorectal cancer cells show vulnerability to inhibition of de novo lipogenesis, indicating that continued lipid production or storage can support survival under treatment-selected conditions (Jog *et al.*, 2025). Conversely, EGFR-tyrosine kinase inhibitor persisters in lung cancer can engage a DPP4-associated program linked to CPT1A and fatty-acid oxidation, again illustrating that increased lipid synthesis and increased lipid oxidation represent distinct metabolic solutions rather than interchangeable manifestations of the same state (Zhang *et al.*, 2025).

Metabolic adaptation is additionally shaped by extracellular metabolites and regulatory coupling across biological levels. Inosine metabolism can promote oxidative adaptation during EGFR-targeted therapy through purinergic signaling, connecting extracellular nutrient availability with intracellular respiratory behavior (Huang *et al.*, 2025). Persister cells can also display H4K20me3-dependent repression linked to one-carbon metabolism and chromatin regulation, showing that metabolic substrate availability may influence a regulatory state that extends beyond immediate ATP generation or redox balance (Ramponi *et al.*, 2025). Such findings caution against treating metabolism as an isolated layer: nutrient processing, enzyme function, signaling, and chromatin organization can become interdependent during persistence.

Functional-genetic studies reinforce the therapeutic relevance of these adaptations while also underscoring their limits. Targeting vulnerabilities identified in persister cells can increase oxidative stress and delay tumor relapse in experimental models, supporting the principle that treatment-tolerant states contain actionable liabilities (Chen, Mainardi, *et al.*, 2024). Redox buffering through PRDX5 has likewise been implicated in the survival of treatment-resistant prostate cancer cells, although this broader resistant-state evidence should not be interpreted as demonstrating a universal DTP mechanism (Wang *et al.*, 2024). Across the available studies, the recurring theme is therefore not a single metabolic signature but a constrained set of biological functions—energy production, redox control, lipid handling, mitochondrial maintenance, and biosynthetic support—that can be achieved through different pathway configurations.

These distinctions are summarized in **Table 2**. The organization deliberately separates biochemical processes that converge functionally but remain mechanistically non-equivalent.

Table 2. Treatment-associated metabolic programs observed in persistent or therapy-resistant tumor-cell states

Metabolic or regulatory unit	Representative treatment context	Principal biochemical function implicated	Directly observed level	Functional interpretation	Main transfer boundary
ACOX1-associated fatty-acid oxidation	BRAF/MEK-targeted melanoma	Utilization of fatty acids during tolerance	Enzyme/pathway and cell state	Supports survival in a defined targeted-therapy persister state	Melanoma and BRAF/MEK context
NPC1L1-linked lipid handling	Chemotherapy-tolerant cancer cells	Cholesterol/lipid adaptation	Protein/pathway and functional response	Contributes to adaptive survival	Mechanism may not extend to unrelated tolerance states
PINK1-mediated mitophagy	Drug-tolerant cancer-cell models	Mitochondrial quality control, respiration and redox homeostasis	Organelle, pathway and functional perturbation	Preserves mitochondrial competence during persistence	Model-dependent mitochondrial reliance
cIGF1R–Parkin–VDAC1 regulation	EGFR-TKI-treated NSCLC	Control of mitophagy and later regrowth competence	Regulatory RNA, protein pathway and cell behavior	Links mitochondrial remodeling with post-treatment fate	EGFR-mutant NSCLC
Lipid-peroxidation-product export	Breast-cancer persisters	Detoxification of reactive lipid products	Transport and redox phenotype	Limits toxic consequences of lipid oxidation	Breast-cancer treatment context
Oxidative phosphorylation	Endocrine-therapy-tolerant ER+ breast cancer	Mitochondrial ATP-generating metabolism	Proteomic, metabolic and functional	Creates a respiratory vulnerability	Endocrine-treatment persister state
Transsulfuration remodeling	BRAF-V600E melanoma	Sulfur metabolism and antioxidant support	Multi-omic and functional	Enhances oxidative-stress management	Targeted-therapy melanoma
De novo lipogenesis	Therapy-resistant colorectal cancer	Lipid biosynthesis and storage	Pathway and functional perturbation	Supports treatment-selected survival	Colorectal-cancer context
DPP4–CPT1A-associated fatty-acid metabolism	EGFR-TKI lung cancer	Fatty-acid oxidation	Protein/pathway and metabolic phenotype	Sustains persister metabolic adaptation	EGFR-targeted lung cancer

Inosine-linked oxidative adaptation	EGFR-targeted lung adenocarcinoma	Purine signaling coupled to respiratory metabolism	Metabolite, signaling and functional response	Connects extracellular metabolite availability to oxidative adaptation	EGFR-targeted setting
One-carbon-linked chromatin regulation	Persister cancer-cell models	Metabolic support of histone methylation state	Metabolic and epigenetic	Couples metabolic supply to transcriptional repression	Mechanistic direction remains model dependent
Redox-buffering vulnerabilities	Multiple resistant/persister models	Control of reactive oxygen species	Genetic, pharmacological and functional	May expose actionable oxidative liabilities	Resistant-state definitions are not interchangeable

Taken together, these findings support a state-transition interpretation in which treatment persistence is maintained by several partially overlapping metabolic solutions, while only a subset has direct evidence connecting them to later recovery. The distinction between mechanisms that preserve viability during treatment and those that remain relevant after drug withdrawal is therefore central to interpreting metabolic persistence.

Figure 1 summarizes metabolic-state continuity and divergence across treatment persistence and early recovery.

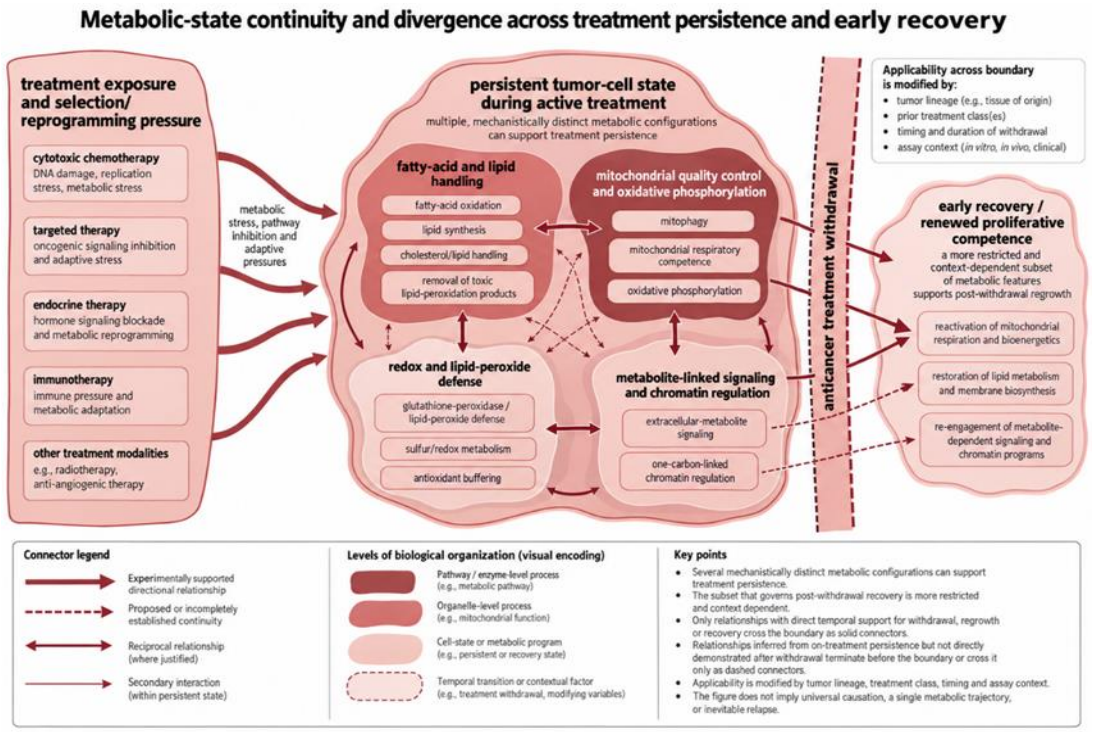


Figure 1. Metabolic-state continuity and divergence across treatment persistence and early recovery

Enzyme Regulation and Proteome Remodeling after Treatment Withdrawal

Post-treatment recovery depends not only on whether a cell survives therapy but on whether its regulatory machinery can restore a proliferative metabolic program. In glioblastoma persisters, PRDM9-dependent chromatin remodeling has been linked to survival together with changes in cholesterol-biosynthetic programs, illustrating how epigenetic regulation can preserve or redirect enzyme-pathway availability during persistence (Joun *et al.*, 2025). Such evidence argues against interpreting metabolite abundance alone as a measure of recovery capacity: the proteomic and chromatin context can determine which metabolic routes remain accessible when treatment pressure changes.

Direct evidence from regrowth experiments sharpens this temporal distinction. DFFB-mediated suppression of interferon signaling has been shown to facilitate persister-cell regrowth, indicating that recovery requires active remodeling of stress-response programs rather than simple release from drug inhibition (Williams *et al.*, 2025). In triple-negative breast cancer, a shared persistence program was observed across multiple treatments and patient-derived systems, whereas relapse-associated cells could shift toward a state more similar to treatment-naïve populations (Baudre *et al.*, 2026). These findings support a reversible, layered model in

which persistence-associated proteomes are remodeled again during recovery.

Mechanisms that govern entry into persistence should therefore be distinguished from those governing exit. Chemotherapy-treated breast-cancer cells can activate WNT signaling to enter a diapause-like early persister state (El Laithy *et al.*, 2026), but this does not establish that WNT signaling is the principal driver of later metabolic reactivation. The temporal position of a pathway within the treatment–withdrawal sequence is consequently as important as its molecular identity.

Table 3 summarizes regulatory and proteomic processes with evidence relevant to post-treatment metabolic recovery.

Table 3. Regulatory and proteomic processes with evidence relevant to post-treatment metabolic recovery

Regulatory or proteomic unit	Treatment context	Biological function supported	Recovery relevance	Principal boundary
PRDM9-linked chromatin remodeling	Glioblastoma persisters	Maintains a persistence-associated regulatory state with cholesterol-program remodeling	May preserve metabolic pathway accessibility	Glioblastoma-specific evidence
DFFB–interferon regulation	Persister-cell regrowth models	Suppresses inflammatory signaling during recovery	Directly linked to renewed growth	Not itself proof of a metabolic mechanism
Shared persistence program in TNBC	Multiple treatment and patient-derived models	Coordinates stress-adapted state features	Demonstrates state remodeling across persistence and relapse	Does not imply complete molecular reversion
WNT-driven diapause-like entry	Chemotherapy-treated breast cancer	Promotes early persister-state entry	Defines an entry mechanism that must be separated from recovery control	No direct evidence that WNT governs post-withdrawal metabolic recovery

Nutrient Dependencies, Metabolic Reactivation, and Recovery of Proliferative Capacity

Recovery from persistence can become limited by the resources required to rebuild redox capacity, mitochondrial function, membrane biomass, and biosynthetic flux. In KRAS-mutant tolerant cells, combined disruption of glutamine metabolism and lysosomal function reduces survival, with metabolomic and rescue evidence supporting a coupled metabolic dependency rather than an isolated nutrient effect (Furukawa *et al.*, 2026). In ovarian cancer, mitochondrial fatty-acid oxidation driven through a CEBPB/HADHA-associated program has been implicated in therapy-resistant survival and recurrence competence (Lin *et al.*, 2026).

Other models show that surviving cells can reallocate rather than simply increase nutrient use. Cisplatin-surviving polyploid cancer cells redirect central carbon sources toward antioxidant metabolism, demonstrating that recovery-associated survival may depend on altered routing of glucose- and glutamine-derived carbon (Li *et al.*, 2026). Colorectal cancer organoids and drug-tolerant cells provide complementary evidence that increasing lipid-peroxidation pressure with docosahexaenoic acid can impair tolerant-cell regrowth through a ferroptosis-linked mechanism (di Blasio *et al.*, 2026).

The specific resource constraint nevertheless varies with treatment and tissue. Cetuximab-tolerant head-and-neck cancer cells can engage FABP1/PPARγ-dependent peroxisomal fatty-acid oxidation (Ling *et al.*, 2026), whereas PARP inhibition in high-grade serous ovarian cancer can produce a redox-dependent dormant reservoir with a distinct pharmacological vulnerability (Suriya *et al.*, 2026). Drug- and immunotherapy-persister populations can also show cross-resistance and shared survival properties without demonstrating identical metabolic wiring (Davern *et al.*, 2026). Nutrient dependence should therefore be interpreted as a context-specific condition for reactivation, not as evidence for one universal recovery fuel.

Table 4 summarizes resource dependencies and experimentally supported vulnerabilities during persistent-cell recovery.

Table 4. Resource dependencies and experimentally supported vulnerabilities during persistent-cell recovery

Resource or metabolic process	Persistent/recovery context	Supported functional role	Vulnerability indicated	Interpretation limit
Glutamine metabolism coupled to lysosomal function	KRAS-mutant tolerant cells	Supports metabolic/redox survival	Dual metabolic–lysosomal targeting	Not a universal glutamine addiction
Mitochondrial fatty-acid oxidation	Therapy-resistant ovarian cancer	Supports survival and recurrence competence	FAO pathway targeting	Proof-of-principle, not clinical recurrence prevention
Central-carbon reallocation	Cisplatin-surviving polyploid cells	Fuels antioxidant metabolism	Disruption of redox-supporting flux	Polyploid survivor state may differ from canonical DTPs

Lipid-peroxidation susceptibility	Colorectal organoids and tolerant cells	Constrains regrowth under oxidative membrane stress	Ferroptosis-promoting intervention	Ex-vivo and treatment-context dependence
Peroxisomal fatty-acid oxidation	Cetuximab-tolerant head-and-neck cancer	Supports persistent-state energy/redox adaptation	FABP1/PPARγ pathway targeting	Tumor- and drug-specific
Redox-dependent dormancy	PARP-inhibited HGSOC	Maintains a dormant survivor reservoir	Context-specific redox targeting	Depends on treatment/genomic background

The combined evidence supports a resource-constrained view of reactivation: successful recovery requires compatible enzyme regulation, proteome organization, organelle function, and nutrient access rather than release from drug pressure alone.

Figure 2 summarizes resource constraints on metabolic reactivation during persistent tumor-cell recovery.

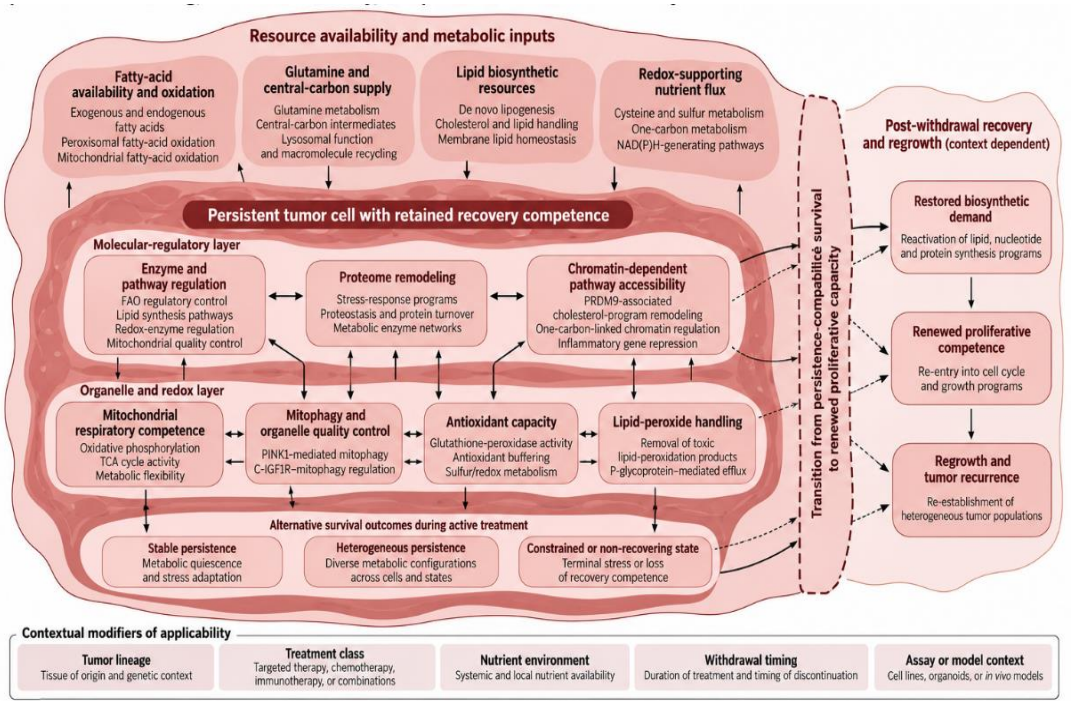


Figure 2. Resource-Constrained Metabolic Reactivation across Enzyme Regulation, Proteome Remodeling, Nutrient Availability, and Persistent Tumor-Cell Recovery

Results and Discussion

Integrated Mechanistic Interpretation, Evidence Gaps, and Therapeutic Implications

Across the literature, metabolic recovery is best interpreted as a conditional transition rather than a fixed persister program. Oxidative and lipid metabolism recur in several models, but ACOX1-dependent fatty-acid oxidation, endocrine-persister oxidative phosphorylation, and DPP4-linked fatty-acid metabolism arise from different upstream contexts and should not be treated as one mechanism (Shen *et al.*, 2020; Tau *et al.*, 2025; Zhang *et al.*, 2025). Their convergence lies at the level of resource use and redox support, not pathway identity.

The same distinction applies to lipid-peroxide control. GPX4 dependency, export of toxic lipid-peroxidation products, and ferroptosis-sensitive regrowth each implicate oxidative membrane damage, yet they act at different biochemical nodes and in different tumor systems (Hangauer *et al.*, 2017; Szebényi *et al.*, 2023; di Blasio *et al.*, 2026). This convergence is therapeutically important because it suggests recurrent stress liabilities while warning against assuming equal efficacy from one intervention across all persistent states.

Temporal evidence is especially decisive. Mitophagy control in EGFR-TKI persisters, DFFB-dependent suppression of interferon signaling during regrowth, and longitudinal remodeling of persistence states in triple-negative breast cancer jointly show that survival during treatment and recovery after withdrawal are separable biological phenotypes (Wang *et al.*, 2023; Williams *et al.*, 2025; Baudre *et al.*, 2026). Future studies should therefore incorporate defined withdrawal intervals, paired measurements during persistence and recovery, and direct regrowth endpoints instead of inferring recovery mechanisms solely from on-treatment measurements.

Important evidence gaps remain. Proteomic abundance is often interpreted without matched enzyme-activity or flux measurements; metabolic phenotypes are frequently established in nutrient-replete culture conditions that may not reproduce tumor resource constraints; and many studies evaluate one treatment and one lineage. The most discriminating experiments would combine longitudinal proteomics, metabolomics or isotope tracing with controlled treatment withdrawal, functional perturbation, rescue, and patient-derived or in-vivo validation. Such designs could distinguish whether a pathway is required to survive therapy, to reactivate after therapy, or for both.

Therapeutically, these findings favor state-aware combination and timing strategies. A metabolic target may be ineffective before a dependency emerges, unnecessary after a state transition, or toxic when applied without tumor-specific context. The practical objective is therefore to identify recovery bottlenecks that are temporally positioned and mechanistically validated in the relevant tumor-treatment setting, rather than to search for a universal persister metabolism.

Conclusion

Persistent tumor cells recover after anticancer treatment only when survival-compatible states can be converted into growth-compatible metabolic states. Current evidence supports multiple routes involving mitochondrial function, redox control, lipid metabolism, nutrient use, chromatin regulation, and proteome remodeling, with substantial dependence on tumor lineage, therapy, and timing. The strongest synthesis is therefore conditional: post-treatment reactivation requires coordinated regulatory and metabolic capacity, but no universal recovery pathway has been established. Future studies that directly compare treatment persistence with defined post-withdrawal recovery will be essential for identifying vulnerabilities that can prevent surviving cells from rebuilding proliferative capacity.

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