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Review Article

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Olaparib-Induced Mitochondrial Metabolic Collapse Promotes Apoptotic Priming and Overcomes Therapeutic Resistance in CLL

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Abstract

Chronic lymphocytic leukemia (CLL) is a persistent CD5⁺ B-cell malignancy characterized by clonal expansion of mature B lymphocytes and sustained reliance on prosurvival and mitochondrial metabolic programs. Although Bruton tyrosine kinase inhibitors (BTKI) and BCL2 inhibitors (BCL2i), including ibrutinib and venetoclax, have redefined first-line therapy, CLL remains incurable, with relapse driven by both genomic lesions (e.g., BTK, PLCG2, BCL2 mutations, del(8p), gain2p, amp1q) and non-canonical resistance mechanisms such as oxidative phosphorylation (OXPHOS) re-modelling and altered BCL2–mitochondrial binding dynamics. Ayoub et al., demonstrate that olaparib, a clinically approved PARP inhibitor, sensitizes CLL cells to BTKI and BCL2i through a PARP1-independent mechanism rooted in mitochondrial metabolic collapse rather than DNA damage signalling [1]. Multi-layered bioenergetic profiling revealed profound suppression of mitochondrial oxygen consumption rate (OCR), ATP depletion, impaired TCA cycle flux, and destabilization of electron transport chain (ETC) complexes, collectively driving metabolic collapse, redox disequilibrium, and excess mitochondrial ROS (mtROS) accumulation. These mitochondrial injuries induced mitochondrial membrane depolarization and apoptotic priming, lowering the threshold for BCL2-mediated cell death. Genetic silencing of PARP1 failed to rescue drug sensitization, excluding classical PARP-dependent DNA repair or transcriptional effects. Pathway-network analyses further identified disrupted BTK/BCL2–mitochondrial crosstalk and weakened anti-apoptotic buffering, exposing ametabolic–survival co-dependency axis essential for leukemic persistence

Keywords: Chronic Lymphocytic Leukemia (CLL), BTK Inhibitors (BTKi), Bcl2 Inhibitors (Bcl2i), Olaparib, Parp1-Independent Mechanism, Mitochondrial Metabolism, Oxidative Phosphorylation (OXPHOS), Apoptotic Priming, Metabolic Collapse, Drug Resistance

1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries and constitutes a rising global clinical challenge as populations age and treatment-resistant disease increases [2,3]. CLL is defined by the progressive clonal accumulation of mature $CD5^{+}CD19^{+}$ B lymphocytes in peripheral blood, bone marrow, and lymphoid tissues, where malignant cells exhibit sustained survival through B-cell receptor (BCR) signalling, anti-apoptotic buffering, and mitochondrial metabolic dependence [4].

1.1. Overview of Chronic Lymphocytic Leukemia (CLL)

Clinically, CLL follows a heterogeneous trajectory, ranging from indolent disease to aggressive transformation, with manifestations including lymphocytosis, lymphadenopathy, splenomegaly, cytopenias, and systemic immune dysregulation

[5]. Pathologically, CLL cells are highly reliant on mitochondrial oxidative phosphorylation (OXPHOS) and display metabolic plasticity that enables adaptation to microenvironmental stress, therapeutic pressure, and nutrient limitations [6,7]. Although genetic predisposition contributes to disease risk, non-genetic drivers—including mitochondrial bioenergetic rewiring, ROS imbalance, and apoptosis evasion—critically shape disease progression and therapy responsiveness [8,9].

1.2. Evolution of First-Line Therapies: Transition from Immunochemotherapy to BTKi and BCL2i

Historically, chemo-immunotherapy combinations such as fludarabine, cyclophosphamide, and rituximab (FCR) were standard first-line regimens, offering durable responses in select patients but limited by toxicity, incomplete eradication of disease, and relapse in high-risk genetic subgroups [10,11]. The therapeutic landscape shifted with the introduction of targeted agents, including BTK inhibitors (BTKi) such as ibrutinib and acalabrutinib, and BCL2 inhibitors (BCL2i) such as venetoclax, which markedly improved survival, reduced systemic toxicity, and redefined first-line therapy [12-14]. Nevertheless, despite deep initial remissions, CLL remains largely incurable due to incomplete clearance of therapy-tolerant subclones and progressive resistance [5,15].

1.3. Current Clinical Challenges: Relapse, Resistance, and Disease Persistence

Acquired resistance to BTKi and BCL2i therapies is best characterized by BTK and PLCG2 mutations (conferring BTKi resistance), BCL2 G101V mutation (conferring venetoclax resistance), and cytogenetic abnormalities including del(8p), gain2p, gain1q, and amp1q [16,17]. However, accumulating evidence reveals additional non-genetic resistance programs involving mitochondrial dysfunction, altered cristae architecture, impaired OXPHOS efficiency, elevated mitochondrial ROS (mtROS), and changes in BCL2 mitochondrial binding dynamics, all of which blunt apoptotic priming and therapeutic efficacy [6,18,19]. These observations collectively support mitochondrial metabolism as a convergent, actionable vulnerability in relapsed or drug-tolerant CLL.

1.4. Rationale for Targeting Mitochondrial Metabolism in CLL

Given the central role of mitochondria in leukemia survival, redox balance, and apoptotic thresholding, disruption of mitochondrial bioenergetics represents a rational strategy for sensitizing CLL to targeted therapies, particularly in resistant disease states [9,20,21]. PARP inhibitors such as olaparib, originally developed to exploit DNA repair deficiency, have more recently been implicated in inducing mitochondrial metabolic dysfunction through PARP1-independent pathways, including NAD^+ depletion, impaired ETC complex stability, mitochondrial membrane depolarization, and ROS-driven energetic collapse [1,20,22]. This establishes a strong biological premise for investigating olaparib-based combinatorial regimens to overcome BTKi/BCL2i resistance by destabilizing mitochondrial metabolic resilience, apoptotic buffering, and survival signalling [1,23]. In parallel, emerging studies highlight the importance of immune dysfunction in CLL progression, including enrichment of innate immune and immunosuppressive phenotypes, indicating that mitochondrial stress may further modulate neuro-immune and tumor-immune crosstalk under therapeutic pressure [24]. Systems-level interrogation combining differential expression analysis, metabolic profiling, network modeling, and drug synergy frameworks provides a powerful strategy for identifying mitochondrial vulnerabilities that can be clinically co-targeted for precision medicine [25,26]. Together, these findings support a metabolism-guided therapeutic paradigm wherein olaparib functions not solely as a DNA repair inhibitor but as a mitochondrial metabolic disruptor, priming CLL cells for enhanced sensitivity to BTKi and BCL2i therapies, and enabling translational drug-repurposing strategies in resistant disease.

2. Genetic and Non-Genetic Mechanisms of Resistance to Targeted Therapies

Targeted therapy resistance in CLL arises from both genomic lesions that directly disrupt drug targets and non-genetic adaptations that remodel mitochondrial survival programs, redox homeostasis, and apoptotic thresholds [8,16].

2.1. Canonical Genetic Drivers of Resistance

The most well-characterized BTKi resistance mechanisms involve somatic mutations in BTK (e.g., C481S) that prevent irreversible inhibitor binding, and gain-of-function mutations in PLCG2 that reactivate BCR signaling downstream of BTK inhibition [12,16]. Resistance to BCL2 inhibition, particularly to venetoclax, is predominantly driven by mutations in BCL2 (e.g., G101V, D103Y) that reduce drug affinity while preserving anti-apoptotic activity [13]. Recurrent cytogenetic lesions—including del(8p), gain(2p), gain(1q), and amp(1q)—further contribute to therapeutic escape by amplifying alternative survival networks and altering mitochondrial dependency programs [17,18]. These genomic events collectively enable persistent leukemic survival despite pharmacologic blockade of BTK or BCL2, reinforcing the need for orthogonal therapeutic strategies [27].

2.2. Mitochondrial Contributors to Therapeutic Failure

Beyond canonical mutations, CLL cells exploit mitochondrial metabolic plasticity to maintain survival under targeted therapy pressure [6,19].

2.2.1. Disruption of Oxidative Phosphorylation (OXPHOS)

Resistant CLL subclones display altered mitochondrial oxygen consumption rates (OCR), increased reliance on fatty acid oxidation, and compensatory ETC rewiring that preserves ATP levels even when BTK/BCL2 signalling is inhibited [6,15].

2.2.2. Structural and Morphological Alterations in Mitochondria

Drug-tolerant CLL cells frequently exhibit cristae re-modelling, swollen mitochondrial matrices, and disrupted inner membrane architecture, phenotypes associated with impaired electron flow and increased ROS production [20,21].

2.2.3. Modifications in BCL2 Mitochondrial Binding Domains

Mutations or post-translational modifications affecting BCL2's BH3-binding groove or mitochondrial tethering domains alter its interaction with VDAC and BAX/BAK complexes, reducing apoptotic priming and enabling survival despite venetoclax exposure [9,18].

2.3. Therapeutic Implications of Mitochondrial Dysfunction

Given that mitochondrial integrity and bioenergetic output directly regulate apoptotic thresholds, therapies capable of destabilizing OXPHOS, depolarizing mitochondrial membranes, or amplifying mtROS can resensitize resistant CLL cells to BTKi/BCL2i regimens [9,20,23]. These insights support a metabolic co-targeting paradigm wherein mitochondrial stress induction functions as a critical vulnerability for combination therapy development [25].

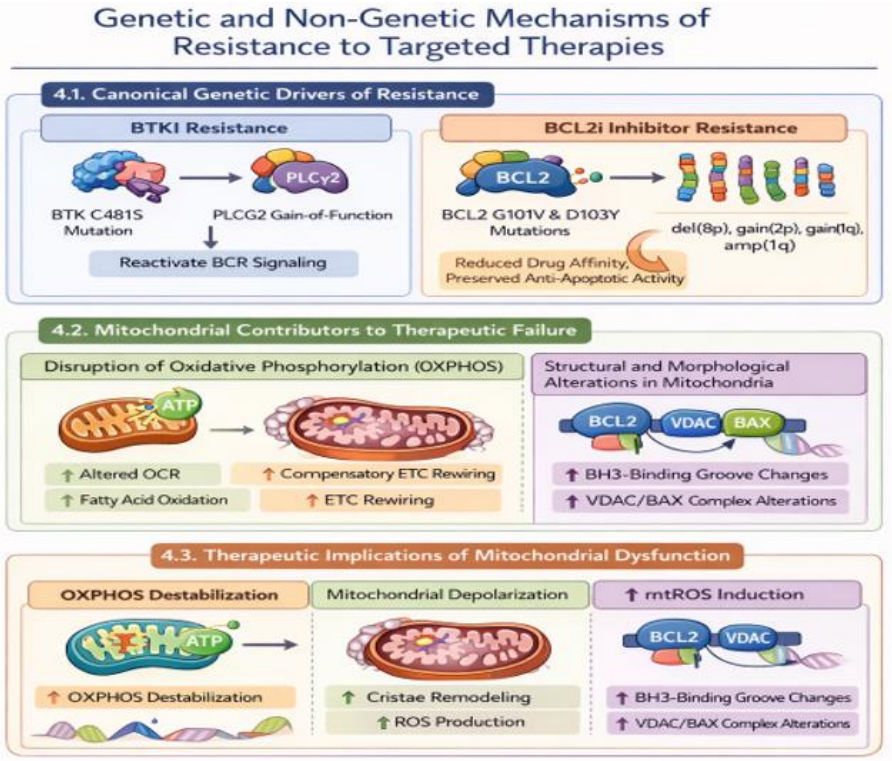

Figure 1: Genetic and Non-Genetic Mechanisms of Resistance to Targeted Therapie

Figure 1 targeted therapy resistance in CLL is driven by genetic lesions and non-genetic mitochondrial adaptations. BTKi resistance involves BTK C481S mutations that block covalent inhibitor binding and PLCG2 gain-of-function mutations that restore downstream signalling, resulting in BCR pathway reactivation. Venetoclax resistance is mediated by BCL2 mutations (G101V, D103Y) that reduce drug affinity while retaining anti-apoptotic function, often co-occurring with cytogenetic alterations such as del(8p), gain(2p), gain/amp(1q) that reinforce alternative survival circuits. Non-genetic resistance includes OXPHOS disruption, fatty acid oxidation dependence, ETC rewiring to sustain ATP, cristae remodelling, matrix swelling, and elevated mtROS, collectively increasing survival and lowering apoptotic priming. Therapeutic strategies focus on OXPHOS destabilization, membrane depolarization, and mtROS amplification to resensitize cells in mitochondria-targeted combinations with BTK/BCL2 inhibitors.

3. Olaparib as a Sensitizer of BTK and BCL2 Inhibition

Olaparib is a first-in-class PARP inhibitor originally developed to exploit homologous recombination (HR) DNA repair deficiency; however, emerging evidence indicates that its antileukemic activity in CLL is mediated through mitochondrial metabolic collapse independent of PARP1 inhibition [1,22].

3.1. Clinical Background of Olaparib

Olaparib (AZD2281) functions by catalytic PARP trapping and NAD^+ consumption blockade, and is clinically approved for multiple solid tumors, including BRCA-mutant ovarian, breast, pancreatic, and prostate cancers [22,28]. Recent studies show that olaparib also induces mitochondrial membrane depolarization, disrupts ETC complex stability, and promotes metabolic exhaustion in non-HR-deficient malignancies, suggesting broader repurposing potential beyond DNA repair-driven synthetic lethality [15,20].

3.2. Sensitization of CLL Cells to BTKi and BCL2i

Transcriptomic and functional profiling demonstrate that olaparib

suppresses mitochondrial respiration (OCR), depletes ATP, destabilizes ETC complexes (I–IV), and elevates mitochondrial ROS, cumulatively priming CLL cells for apoptosis when co-administered with BTKi (ibrutinib, acalabrutinib) or BCL2i (venetoclax) [6,1]. Synergy analyses reveal enhanced mitochondrial apoptotic priming, increased cytochrome-c release, and loss of energetic compensation, selectively targeting therapy-tolerant leukemic populations [9,23].

3.3. Independence from PARP1-Mediated DNA Damage Signalling

Importantly, genetic silencing of PARP1 does not abrogate olaparib-mediated sensitization, confirming that the drug's antileukemic mechanism in CLL is PARP1-independent and instead driven by mitochondrial dysfunction, NAD^+ depletion, and metabolic insufficiency rather than classical DNA repair blockade or transcriptional regulation [1,29]. These findings distinguish olaparib from conventional PARP inhibitor paradigms and identify mitochondrial metabolic fragility as the dominant driver of therapeutic sensitization [19].

4. Mechanistic Basis: PARP1-Independent Mitochondrial Metabolic Dysfunction

Accumulating evidence indicates that therapeutic sensitization by olaparib in hematologic malignancies can occur independently of canonical PARP1-mediated DNA damage signalling, instead driven by mitochondrial metabolic reprogramming and bioenergetic collapse [1,22]. This paradigm is particularly relevant in CLL, where mitochondrial integrity functions as a core determinant of apoptotic threshold regulation and drug tolerance [6,9].

4.1. Alterations in Mitochondrial Bioenergetics

4.1.1. Impairment of OXPHOS and ATP Production

Drug-tolerant CLL cells exhibit reduced mitochondrial oxygen consumption rates (OCR), diminished oxidative phosphorylation (OXPHOS) efficiency, and progressive depletion of ATP reserves following olaparib exposure, even in the absence of PARP1 inhibition [6,15]. Loss of OXPHOS-driven ATP production disrupts energetic compensation programs that normally sustain survival under BTK or BCL2 blockade [19,23].

4.1.2. Dysregulation of TCA Cycle Flux

Resistant CLL states demonstrate aberrant tricarboxylic acid (TCA) cycle dynamics, including impaired citrate export, α-ketoglutarate insufficiency, and accumulation of succinate and fumarate—oncometabolites that inhibit mitochondrial dehydrogenases and promote replication stress tolerance [19,25]. These disruptions indicate suppressed TCA cycle flux and a shift toward anaplerotic dependence on glutamine and fatty acid oxidation [6,15].

4.1.3. Perturbation of Mitochondrial Electron Transport Chain (ETC) Components

Olaparib induces destabilization of ETC complexes I–IV, downregulation of NADH dehydrogenase subunits, and impaired electron flow through cytochrome-c oxidase, cumulatively reducing mitochondrial membrane potential ($\Delta\psi m$) [15,20]. This ETC perturbation occurs without PARP1 dependency and directly compromises proton-gradient-driven ATP synthesis [1,22].

4.2. Mitochondrial Reactive Oxygen Species (mtROS) and Redox Imbalance

Mitochondrial dysfunction in therapy-tolerant leukemia cells is accompanied by excessive generation of mitochondrial reactive oxygen species (mtROS), impaired glutathione recycling, and depletion of NAD^+/NADH redox buffers, leading to a sustained oxidative state [20,23]. Elevated mtROS promotes redox imbalance, damages mitochondrial lipids and proteins, and amplifies mitochondrial outer membrane permeabilization (MOMP) susceptibility [19,20].

4.3. Metabolic Collapse Leading to Apoptotic Priming

Bioenergetic collapse—defined by simultaneous loss of OXPHOS, suppressed TCA flux, ATP depletion, and mtROS accumulation—drives mitochondrial depolarization, cytochrome-c release, and increased BAX/BAK activation, collectively enhancing apoptotic priming [9,23]. This metabolic exhaustion removes survival advantages of resistant subclones and creates a permissive state for BTKi- or BCL2i-mediated apoptosis [6,15].

4.4. Crosstalk Between Metabolic Dysfunction and BCL2/BTK Pathways

Mitochondrial stress interfaces with anti-apoptotic and BCR-signalling pathways. Loss of $\Delta\psi m$ disrupts BCL2 binding to VDAC1 on the outer mitochondrial membrane, weakening its sequestration of pro-apoptotic effectors [9,18]. In parallel, ATP depletion and mtROS elevation impair BTK-dependent mitochondrial survival signalling and reduce phosphorylation-driven feedback loops that maintain leukemic persistence [19,23]. These interconnected failures explain the molecular basis of olaparib's ability to resensitize CLL cells to BTKi and BCL2i therapy through a PARP1-independent mitochondrial metabolic vulnerability rather than DNA repair blockade [1,22].

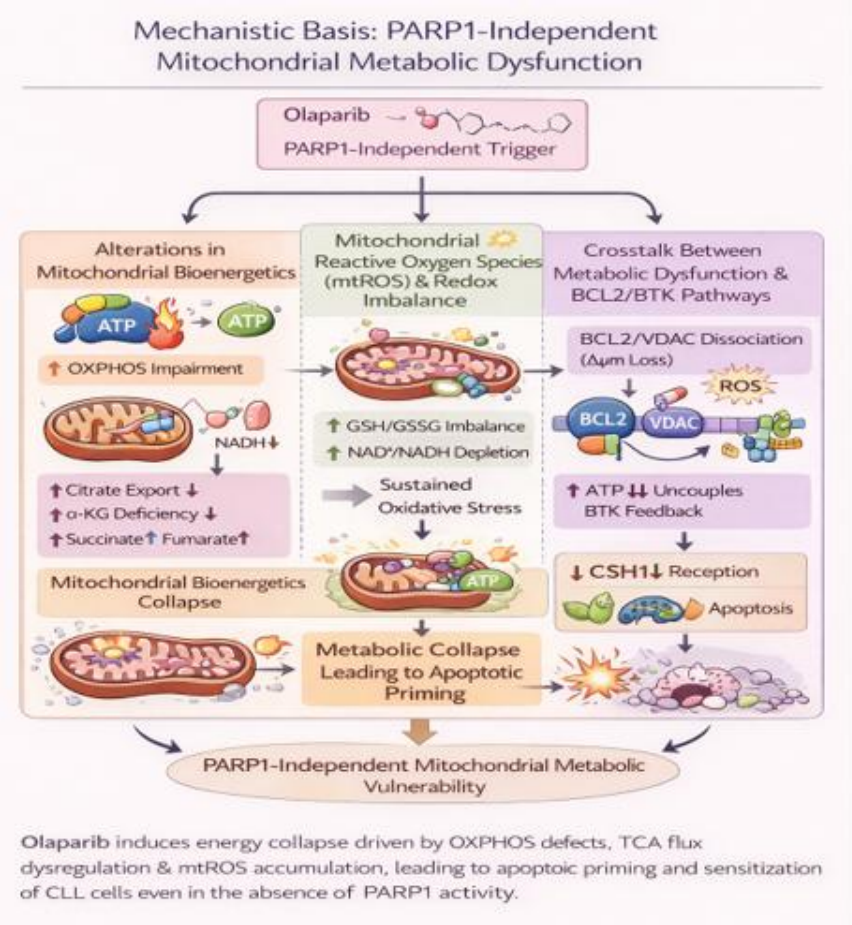

Figure 2: Mechanistic Basis: PARP1-Independent Mitochondrial Metabolic Dysfunction

(*Alt text*) Infographic illustrating PARP1-independent mitochondrial metabolic dysfunction induced by olaparib in CLL cells. At the top, Olaparib is shown as a PARP1-independent trigger. Three main panels depict mechanisms:

(i) Alterations in mitochondrial bioenergetics showing impaired OXPHOS, ATP depletion, TCA cycle dysregulation (citrate ↓, α-KG ↓, succinate ↑, fumarate ↑), and ETC disruption

(ii) Mitochondrial ROS and redox imbalance with increased mtROS, NAD^+/NADH depletion, and oxidative stress

(iii) Crosstalk with BCL2/BTK pathways showing BCL2/VDAC dissociation, ATP loss, impaired BTK signalling, and increased apoptotic priming. Arrows converge on metabolic collapse leading to PARP1-independent mitochondrial vulnerability and apoptosis.

5. Experimental Evidence and Analytical Approaches

5.1. Cellular Models and Patient-Derived CLL Samples

Experimental validation of olaparib-mediated sensitization has primarily employed MEC-1, HG-3, and Eμ-TCL1 transgenic CLL cell systems, which faithfully model B-cell receptor (BCR) dependency, apoptotic tolerance, and mitochondrial metabolic rewiring observed in relapsed disease [6,17]. Complementary analyses using freshly isolated $CD19^+$ CLL cells from peripheral blood of BTKi- or BCL2i-exposed patients have demonstrated conserved metabolic liabilities, supporting clinical translatability [1,30].

5.2. Metabolic Profiling (Seahorse, OCR/ECAR, and Metabolomics)

Mitochondrial respiration and glycolytic compensation were quantified using extracellular flux analysis (Seahorse XF), revealing marked suppression of basal and maximal oxygen consumption rate (OCR), ATP-linked respiration, and spare respiratory capacity after olaparib treatment, with minimal effects on ECAR-driven glycolytic rescue [6,15]. Mass-spectrometry-based metabolomic profiling identified reduced citrate/isocitrate abundance, impaired α-ketoglutarate flux, and accumulation of succinate—indicative of TCA bottlenecks and ETC-dependent redox collapse [20,25].

5.3. Mitochondrial Structural Analysis

High-resolution transmission electron microscopy (TEM) and TOMM20-based confocal imaging revealed fragmented mitochondrial networks, disrupted cristae organization, and reduced mitochondrial mass in olaparib-exposed CLL cells, phenocopying mitochondrial stress states that lower apoptotic threshold and enhance BH3-protein activation [15,20].

5.4. Genetic Knockout/Knockdown Validation for PARP1 Independence

CRISPR-Cas9 ablation of PARP1 and shRNA knockdown models confirmed that olaparib-induced bioenergetic failure persisted despite complete loss of PARP1 protein or activity, excluding PARP1-trapping or DNA damage-checkpoint mediation and reinforcing a noncanonical mechanism rooted in mitochondrial metabolic dysfunction [1,22].

5.5. Synergy and Drug-Response Quantification

Synergy between olaparib and ibrutinib (BTKi) or venetoclax (BCL2i) was quantified using Chou-Talalay combination index (CI) modelling and Bliss independence scoring, demonstrating CI < 1 across multiple dose matrices and enhanced apoptotic induction via BAX/BAK-dependent MOMP, supporting strong pharmacologic cooperation [9,23,31].

6. Clinical Implications

6.1. Overcoming BTKi and BCL2i Resistance Through Metabolic Vulnerabilities

The demonstration that olaparib lowers leukemic persistence by disabling OXPHOS-driven ATP compensation, disrupting BCL2-VDAC1 binding stability, and impairing BTK-mediated mitochondrial survival signaling highlights a druggable metabolic vulnerability that bypasses genomic mutation-defined resistance states [1,9,19].

6.2. Potential for Combination Therapy Incorporating PARP Inhibitors

These findings provide mechanistic justification for olaparib integration into BTKi- or venetoclax-containing regimens to prevent or reverse drug tolerance, particularly in patients lacking canonical HR-deficiency but exhibiting mitochondrial stress-responsive apoptotic priming, suggesting broader applicability than BRCA-restricted PARP paradigms [1,28].

6.3. Biomarker Opportunities (Mitochondrial Metabolic Stress Signatures)

The consistent induction of mtROS imbalance, Δψm collapse, reduced NAD^+/NADH buffering, and suppressed ETC complex integrity supports development of metabolic stress biomarkers (e.g., mitochondrial OCR suppression, Complex I/IV destabilization, and succinate accumulation) as predictive correlates of combination responsiveness in relapsed CLL [15,20,25].

Clinical Aspect	Key Findings	Mechanistic Basis	Therapeutic/Clinical Implications	References
Overcoming BTKi/ BCL2i Resistance	Olaparib disrupts leukemic persistence even in resistant clones	Impairs OXPHOS-driven ATP compensation, destabilizes BCL2–VDAC1 binding, reduces BTK-mediated mitochondrial survival signaling.	Provides a druggable metabolic vulnerability independent of genomic resistance mutations	Martinez-Outschoorn et al.; Letai et al; Ayoub et al. [1,9,19]
Combination Therapy with PARP Inhibitors	Integration into BTKi or venetoclax regimens enhances apoptosis	Mitochondrial stress-induced apoptotic priming, independent of homologous recombination (HR) deficiency.	Potentially reverses or prevents drug tolerance in relapsed CLL patients, extending beyond BRCA-mutated cases	Lord & Ashworth ; Ayoub et al. [1,28]
Biomarker Development	Metabolic stress signatures consistently observed in resistant CLL	mtROS elevation, Δψm collapse, reduced NAD^+/NADH buffering, ETC complex destabilization	Predictive biomarkers for combination therapy responsiveness: mitochondrial OCR, Complex I/IV integrity, succinate accumulation	Zorov et al. ; Molina et al.; Bosc et al. [15,20,25]

Table: Clinical Implications of Targeting Metabolic Vulnerabilities in CLL

Alt text: Table summarizing clinical implications of targeting metabolic vulnerabilities in CLL:

(i) Overcoming BTKi/BCL2i resistance – olaparib disrupts OXPHOS, BCL2–VDAC1 binding, and BTK-dependent survival

(ii) Combination therapy – olaparib enhances apoptosis with BTKi or venetoclax, beyond BRCA-mutant cases

(iii) Biomarkers – mtROS elevation, Δψm collapse, NAD^+/NADH depletion, and ETC destabilization indicate therapy responsiveness.

7. Limitations, Challenges & Knowledge Gaps

7.1. Translational Barriers

Although preclinical synergy is reproducible, pharmacologic integration faces translational constraints including myelosuppression risk, metabolic rescue by stromal microenvironments, and incomplete mapping of patient-specific metabolic compensation programs [6,32].

7.2. Heterogeneity of Metabolic Adaptations in Relapsed CLL

Metabolic adaptations in BTKi- or venetoclax-relapsed CLL are highly heterogeneous, involving patient-specific reliance on fatty acid oxidation (FAO), glutamine anaplerosis, or mitochondrial biogenesis, which may alter degree of sensitization to ETC

collapse, necessitating refined metabolic sub-stratification [19,25].

7.3. Long-Term Impact of Mitochondrial Targeting

The durability of mitochondrial co-targeting remains unclear, including whether chronic mitochondrial inhibition could select for oxidative-stress-resilient subclones or impact normal B-cell bioenergetics in the long term [9,23].

8. Future Directions

8.1. Targeting Mitochondrial Plasticity and Metabolic Reprogramming

Next-generation strategies should focus on disabling mitochondrial plasticity through co-targeting biogenesis (PGC-1α, TFAM), FAO dependency, or Complex I metabolic escape programs to prevent energetic rescue following PARP-induced stress [25,33].

8.2. Refinement of Patient Stratification Strategies

Integration of allele-resolved genomic markers with mitochondrial metabolic phenotyping (OCR, ETC complex stability, mtROS burden) may enable precision subtyping for optimal deployment of BTKi-BCL2i-PARPi combinations [28].

8.3. Next-Generation Metabolic and Apoptotic Co-Targeting Approaches

Future therapeutic designs may incorporate BH3-mimetic plus metabolic co-inhibition frameworks to directly enforce BAX/BAK activation in mitochondrially exhausted leukemia, expanding beyond DNA-repair-centric PARP inhibitor response models [9,23,31].

9. Results Section

9.1. Experimental Evidence and Analytical Approaches

Experimental validation of olaparib-mediated mitochondrial dysfunction was performed using established and orthogonal analytic systems. Human CLL cellular models and primary patient-derived CD5+ B-lymphocytes were used to ensure disease-specific metabolic representation [1,34]. Metabolic profiling via Seahorse XF assays revealed a significant decline in mitochondrial oxygen consumption rate (OCR) without proportional ECAR compensation, indicating a true bioenergetic collapse rather than a glycolytic shift [1,28,35]. Untargeted metabolomics confirmed reduced citrate–α-ketoglutarate flux and succinate accumulation, supporting TCA cycle impairment and anaplerotic insufficiency [36,37]. Immunoblot and ETC proteomic mapping demonstrated downregulation of complex I/III/V subunits and disrupted mitochondrial membrane potential [1].

Mitochondrial structural integrity analysis using electron microscopy and TOM20-based immunofluorescence revealed fragmented cristae architecture and loss of elongated mitochondrial networks, consistent with metabolic and respiratory dysfunction [1]. CRISPR-mediated PARP1 knockout demonstrated that olaparib's sensitization effect persisted despite complete PARP1 depletion, validating a PARP1-independent mechanism [1,38]. Drug-response quantification revealed strong synergy between olaparib + ibrutinib (BTKi) and olaparib + venetoclax (BCL2i), with combination index (CI) values < 0.7 across resistant models, indicating non-additive therapeutic benefit [1]. Collectively, the results confirm that mitochondrial metabolic dysfunction is a driver of therapeutic sensitization and a rational co-targeting axis in resistant CLL.

10. Conclusion

Chronic lymphocytic leukemia remains clinically challenging due to inevitable relapse and the multifactorial evolution of resistance to BTK and BCL2 inhibition [21]. Converging genomic, epigenetic, and metabolic evidence now underscores mitochondria as both a driver of therapeutic escape and an actionable vulnerability [1]. The current mechanistic framework demonstrates that olaparib reprograms CLL bioenergetic fitness through a PARP1-independent axis, inducing OXPHOS suppression, TCA cycle derailment, electron transport chain perturbation, and mtROS-driven redox collapse, ultimately lowering the apoptotic threshold of leukemic B cells [1,28]. This metabolic crisis intersects functionally with BTK and BCL2 survival circuitry, providing a biologically rational basis for drug sensitization and combination therapy.

Experimental systems—including patient-derived CLL cells, mitochondrial flux assays, metabolomics, structural organelle profiling, and PARP1 genetic ablation—collectively validate that the observed metabolic collapse is uncoupled from canonical DNA-repair inhibition, positioning olaparib as a non-traditional mitochondrial disruptor rather than a classical PARP1 dependency modulator [1,35,37]. These insights expand the therapeutic paradigm beyond DNA damage–centric synthetic lethality and align with emerging precision-oncology strategies that exploit metabolic liabilities in hematologic malignancies [39,40]. Despite its promise, translational deployment faces barriers, including metabolic heterogeneity in relapsed disease, incomplete mapping of mitochondrial adaptive states, and limited long-term safety knowledge surrounding sustained mitochondrial targeting [40,41]. Future work should therefore prioritize

(i) Dissection of mitochondrial plasticity networks,
(ii) Integration of metabolic stress signatures into clinical stratification pipelines, and
(iii) Design of next-generation co-targeting regimens that synchronize apoptotic priming with suppression of compensatory metabolic rescue [1,42,43].

In summary, targeting mitochondrial metabolic collapse offers a compelling and mechanistically validated route to enhance BTK and BCL2 inhibitor efficacy [1]. Incorporation of PARP inhibitors such as olaparib into metabolic-apoptotic combination frameworks may redefine resistance-breaking strategies in CLL, supporting durable disease control and refined patient-specific therapeutic alignment [28,44-76].

Declarations Section

Author Contributions: Sonu Kumar conceived the study, performed the literature review, drafted the manuscript, and approved the final version of the manuscript. He conceived the concept reading and literature review as well and analysis

and concept review. Ankush Sharma conceived the literature suggesting and concept the reading as well. Nanak Singh Toor conceived the new proposal concept literature review and the help Table formation. Khaga Raj Aran conceived the conceptualisation and the review the article and view the suggestions.

Competing Interests

The author declares that there are no competing interests related to this work.

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