# Targeting DNA Damage Repair with PARP Inhibitors: Metabolomic and Cytotoxic Insights for Cholangiocarcinoma Therapy

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**Background and Objective:** Cholangiocarcinoma (CCA) is an aggressive cancer with a poor prognosis and limited therapeutic options. DNA damage repair (DDR) pathways are important for tumor cell survival. Inhibition of poly (ADP-ribose) polymerase (PARP) has emerged as a promising therapeutic approach, particularly in cancers with BRCA deficiency mutation. This study is to investigate the therapeutic potential of PARP inhibitors in CCA, focusing on cytotoxic effects and metabolomic alterations as indicators of treatment response.

**Methods:** CCA cell lines (KKU-023, KKU-452) were treated with PARP inhibitors (PARPi; Niraparib, Olaparib) to assess cytotoxicity via MTT and clonogenic assays then migration was assessed using transwell migration assay. In parallel, metabolomic profiling was performed using LC–MS to identify metabolic changes induced by PARPi. Bioinformatic analyses were conducted by MS-dial and MetaboAnalyst to explore pathway enrichment and potential metabolic vulnerabilities

**Results:** PARP inhibitors (PARPi) demonstrated a significant reduction in cell viability across cholangiocarcinoma (CCA) cell lines in a dose-dependent manner. Among the tested compounds, Niraparib exhibited superior efficacy against CCA cells compared to Olaparib, as evidenced by lower IC50 values. A comparative analysis of PARPi cytotoxicity between BRCA wild-type (KKU-452) and BRCA-mutant (KKU-023) CCA cells revealed enhanced sensitivity in the BRCA-mutant cell line. PARPi treatment substantially impaired cellular migration and clonogenic survival capacity, which corroborated its cytotoxic efficacy. Comprehensive metabolomic profiling elucidated alterations in several critical biochemical pathways, including β-oxidation of long-chain fatty acids, purine metabolism, methionine metabolism, and sphingolipid metabolism, suggesting that metabolic reprogramming is associated with response to PARP inhibition. The integration of cytotoxicity data with metabolomic findings indicates that PARP inhibition not only compromises DNA repair mechanisms but also disrupts cellular energy homeostasis, potentially augmenting therapeutic sensitivity.

**Conclusions:** This study provides novel insights into the dual role of PARP inhibitors in CCA, demonstrating both cytotoxic and metabolomic effects. These findings support the rationale for PARP-targeted therapy in cholangiocarcinoma and highlight potential metabolic signaling pathways that may affect PARPi sensitivity.

**Keywords:** PARP inhibitors, cholangiocarcinoma; DNA damage repair, cytotoxicity, metabolomics

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