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BRCA1-MTOR CROSSTALK IN BREAST CANCER

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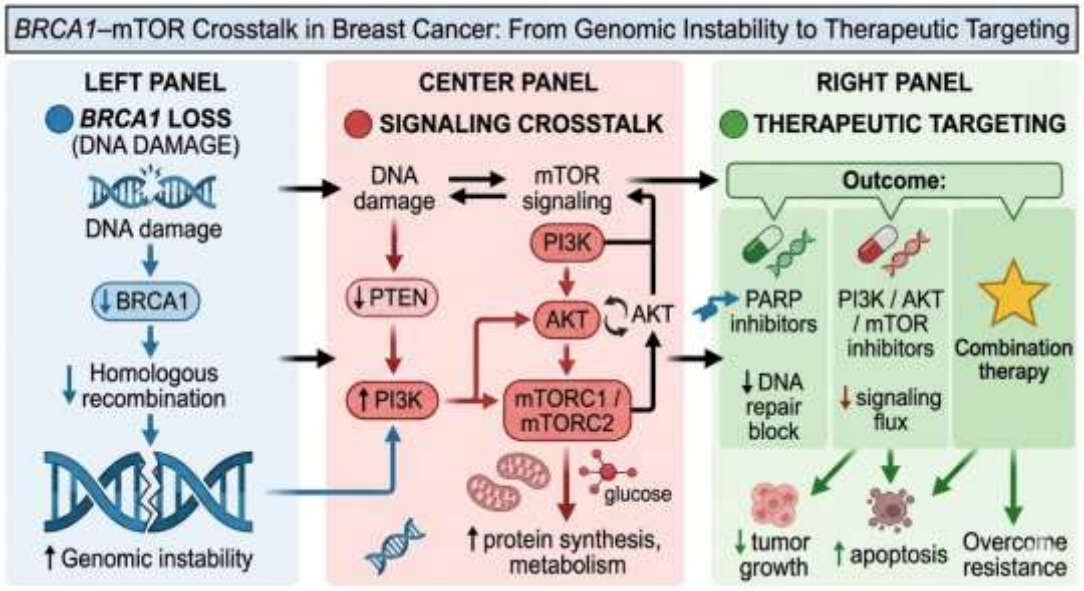
Abstract:
Breast cancer arises from the interplay of genomic stability pathways and metabolic signaling networks. The tumor suppressor BRCA1, which plays a critical role in regulating DNA damage repair, and the mechanistic target of rapamycin (mTOR), which regulates cell growth and metabolism, have generally been studied However, growing evidence suggests a functional cross-talk between BRCA1 and mTOR signaling in breast cancer. BRCA1 deficiency not only impairs homologous recombination-based DNA repair but also stimulates mTOR signaling by suppressing the PI3K/AKT pathway, resulting in increased anabolic Conversely, mTOR signaling can regulate BRCA1 function by post-translationally modifying it and through stress responses, indicating a bidirectional regulation This review summarizes the current understanding of mechanistic insights of the BRCA1-mTOR signaling interface focusing on key regulatory nodes, feedback loops and context-dependent interactions. We also discuss the therapeutic potential of blocking this crosstalk, including PARP inhibitor and mTOR inhibitor combinations. Knowing this integrated signaling network may lead to new mechanism-based treatments in breast cancer.

KEYWORDS: BRCA1; mTOR signaling, breast cancer, DNA damage repair, PI3K/AKT pathway; therapeutic resistance; PARP inhibitor; targeted therapy

GRAPHICAL ABSTRACT:



1. INTRODUCTION

Breast cancer is a highly heterogeneous malignancy driven by complex interactions between genomic instability and dysregulated signaling networks that govern cellular proliferation, survival, and metabolism. Increasing evidence indicates that tumor progression is not solely dictated by genetic alterations but also by the integration of DNA damage response pathways with metabolic signaling cascades that enable tumor adaptation and therapeutic resistance[1-3]. Among the critical regulators of these processes, the breast cancer susceptibility protein BRCA1 and the mechanistic target of rapamycin (mTOR) pathway have emerged as key determinants of tumor biology.

BRCA1 plays a central role in maintaining genomic integrity through its involvement in homologous recombination-mediated DNA repair, cell cycle checkpoint regulation, and chromatin remodelling[4-6]. Loss or mutation of BRCA1 results in defective DNA repair, accumulation of genomic instability, and increased susceptibility to tumorigenesis, particularly in aggressive breast cancer subtypes such as triple-negative breast cancer[7, 8]. In contrast, the PI3K/AKT/mTOR signaling pathway is a major regulator of cellular growth and metabolism and is frequently hyperactivated in breast cancer due to genetic alterations such as PIK3CA mutations

or PTEN loss[9-11]. Activation of this pathway promotes protein synthesis, cell survival, and metabolic reprogramming, thereby supporting tumor progression.

Emerging studies suggest that BRCA1 and mTOR signaling are functionally interconnected rather than operating as independent pathways. BRCA1 deficiency has been shown to enhance the PI3K/AKT/mTOR axis, which also regulates processes such as epithelial-mesenchymal transition, inhibition of apoptosis, and translational control, which collectively contribute to tumor aggressiveness[15, 16]. Conversely, mTOR signaling can influence DNA damage response mechanisms by regulating protein translation and post-translational modification of repair-associated proteins, suggesting a bidirectional regulatory relationship between these pathways[17, 18].

Importantly. Dysregulation of the PI3K/AKT/mTOR pathway has been implicated in resistance to endocrine therapy, chemotherapy, and targeted agents, underscoring its clinical relevance[19, 20]. Recent findings further indicate that aberrant mTOR signaling contributes to metabolic plasticity and poor clinical outcomes in breast cancer patients[21]. Despite extensive characterization of BRCA1 and mTOR pathways individually, the mechanistic basis and biological significance of their crosstalk remain incompletely understood.

In this review, I provide a mechanistic overview of the BRCA1-mTOR signaling interface in breast cancer, focusing on key regulatory nodes, feedback mechanisms, and context-dependent interactions that integrate genomic stability with metabolic control. I further discuss the therapeutic implications of targeting this crosstalk, with an emphasis on combination strategies aimed at overcoming resistance and improving treatment outcomes.

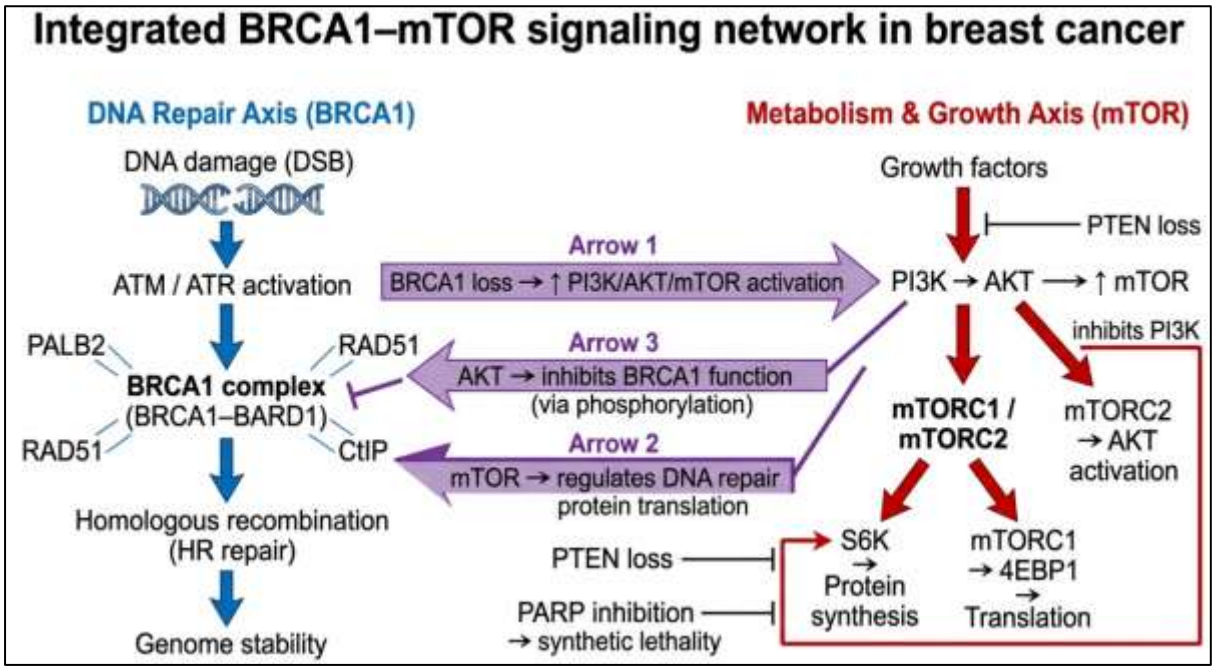


Figure 1: Integrated BRCA1-mTOR signaling network in breast cancer

Schematic representation of the bidirectional crosstalk between BRCA1-mediated DNA damage response and PI3K/AKT/mTOR signaling in breast cancer. DNA double-strand breaks activate ATM/ATR kinases, leading to recruitment of the BRCA1–BARD1 complex and associated factors (PALB2, RAD51, CtIP) to facilitate homologous recombination and maintain genomic stability. In parallel, growth factor signaling activates the PI3K/AKT pathway, which is negatively regulated by PTEN; loss of PTEN results in sustained activation of AKT and downstream mTOR complexes (mTORC1 and mTORC2). mTORC1 promotes protein synthesis through S6K and 4EBP1, while mTORC2 enhances AKT activation, establishing a positive feedback loop. Crosstalk mechanisms include BRCA1 loss–mediated activation of PI3K/AKT/mTOR signaling, mTOR-dependent regulation of DNA repair protein translation, and AKT-mediated inhibition of BRCA1 function via phosphorylation. Feedback regulation through S6K and compensatory AKT activation is also depicted. Therapeutic targeting of this axis is highlighted, where PARP inhibition induces synthetic lethality in BRCA1-deficient tumors, and PI3K/AKT/mTOR inhibition suppresses oncogenic signaling, underscoring the cooperative role of these pathways in tumor progression and therapeutic resistance. [19-21]

2. Biology of BRCA1 in Breast Cancer

BRCA1 is a multifunctional tumor suppressor that plays a central role in maintaining genomic stability through its involvement in DNA damage repair, cell cycle regulation, transcriptional control, and chromatin remodeling. The BRCA1 protein contains an N-terminal RING domain that mediates ubiquitin ligase activity and a C-terminal BRCT domain responsible for phosphoprotein binding, enabling its participation in multiple protein complexes essential for genome maintenance[22-24].

A primary function of BRCA1 is its role in homologous recombination (HR)-mediated DNA double-strand break (DSB) repair. Upon DNA damage, BRCA1 is recruited to sites of damage through ATM/ATR-dependent

signaling and forms complexes with BARD1, PALB2, and BRCA2 to facilitate RAD51 loading and strand invasion[25-28]. This process ensures high-fidelity repair of DSBs, thereby preventing genomic instability. Loss of BRCA1 function impairs HR repair, resulting in reliance on error-prone repair pathways such as non-homologous end joining (NHEJ), which contributes to mutation accumulation and tumorigenesis[29, 30].

Beyond DNA repair, BRCA1 plays a critical role in cell cycle checkpoint regulation, particularly at the G1/S and G2/M transitions. BRCA1 interacts with checkpoint kinases such as CHK1 and CHK2 and regulates p53-dependent transcriptional responses, thereby coordinating DNA repair with cell cycle progression[31-33]. Disruption of these checkpoints in BRCA1-deficient cells promotes uncontrolled proliferation despite the presence of DNA damage.

BRCA1 is also involved in chromatin remodeling and transcriptional regulation through interactions with histone modifiers and transcription factors. It regulates the expression of genes involved in DNA repair, apoptosis, and cell cycle control, thereby contributing to tumor suppression at multiple levels[34, 35]. Additionally, BRCA1 has been implicated in the regulation of oxidative stress and cellular metabolism, suggesting a broader role in maintaining cellular homeostasis[36].

Importantly, germline mutations in BRCA1 are strongly associated with hereditary breast and ovarian cancers, with BRCA1-mutated tumors often exhibiting basal-like or triple-negative phenotypes characterized by high genomic instability and aggressive clinical behaviour[37-39]. These tumors display increased sensitivity to DNA-damaging agents and poly) ADP-ribose) polymerase (PARP) inhibitors due to synthetic lethality arising from HR deficiency[40. 41].

Recent studies further indicate that BRCA1 deficiency influences additional oncogenic signaling pathways, including PI3K/AKT/mTOR, thereby linking genomic instability with metabolic reprogramming[42-44]. This functional interplay highlights the broader significance of BRCA1 beyond DNA repair and underscores its role as a central node in tumor biology.

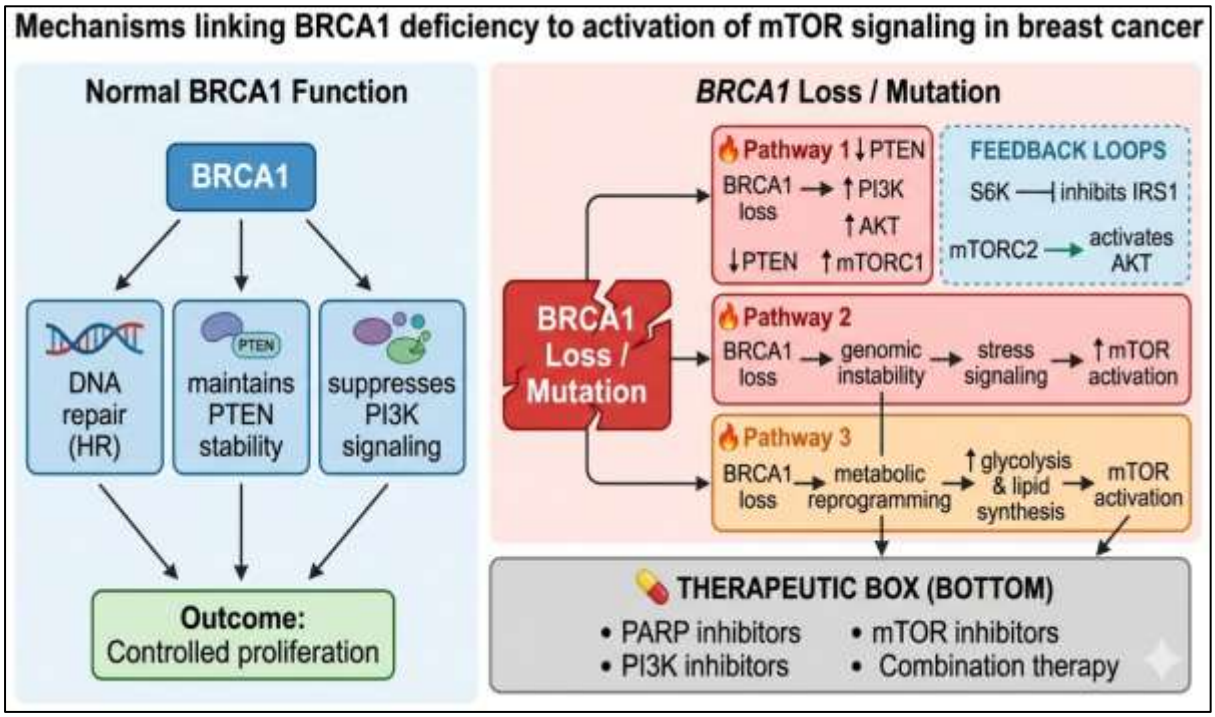


Figure 2: Mechanism linking BRCA1 deficiency to activation of mTOR signaling in breast cancer

Schematic illustration of the molecular mechanisms by which BRCA1 loss or mutation drives activation of the PI3K/AKT/mTOR signaling pathway in breast cancer. Under normal conditions (left panel), BRCA1 maintains genomic stability by facilitating homologous recombination (HR)-mediated DNA repair, stabilizing PTEN, and suppressing PI3K signaling, thereby ensuring controlled cellular proliferation. In contrast, BRCA1 deficiency (right panel) promotes mTOR activation through multiple interconnected pathways. In Pathway 1, loss of BRCA1 reduces PTEN stability, leading to enhanced PI3K/AKT signaling and subsequent activation of mTORC1. In Pathway 2, BRCA1 deficiency induces genomic instability, triggering stress-responsive signaling cascades that further stimulate mTOR activity. In Pathway 3, BRCA1 loss drives metabolic reprogramming, characterized by increased glycolysis and lipid synthesis, which supports mTOR activation and tumor growth. Feedback regulation is also depicted, including S6K-mediated inhibition of IRS1 and mTORC2-dependent activation of AKT, forming regulatory loops that sustain pathway activation. The therapeutic box highlights potential intervention strategies targeting this axis, including PARP inhibitors, PI3K inhibitors, mTOR inhibitors, and combination therapies. Collectively, this figure illustrates how BRCA1 deficiency integrates genomic instability, metabolic adaptation, and oncogenic signaling to promote breast cancer progression[22-44].

3. mTOR Signaling in Breast Cancer

The mechanistic target of rapamycin (mTOR) is a highly conserved serine/threonine kinase that functions as a central regulator of cellular growth, metabolism, proliferation, and survival. The mTOR integrates signals from growth factors, nutrients, energy status, and stress conditions to coordinate anabolic and catabolic processes essential for tumor progression[45-47].

mTOR exists in two structurally and functionally distinct multiprotein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1, defined by the presence of regulatory-associated protein of mTOR (Raptor), primarily regulates protein synthesis through phosphorylation of downstream effectors such as ribosomal protein S6 kinase (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4EBP1). Activation of mTORC1 promotes cap-dependent translation, lipid biosynthesis, and nucleotide synthesis, thereby supporting rapid cellular proliferation[48-50]. In contrast, mTORC2, characterized by the presence of Rictor, regulates cytoskeletal organization and phosphorylates AKT at Ser473, thereby enhancing AKT signaling and promoting cell survival[51, 52].

Upstream, mTOR signaling is tightly regulated by the PI3K/AKT pathway, which is frequently dysregulated in breast cancer. Activation of receptor tyrosine kinases stimulates PI3K, leading to the production of phosphatidylinositol-3, 4, 5-trisphosphate (PIP3) and subsequent activation of AKT. Activated AKT phosphorylates and inhibits the tuberous sclerosis complex (TSC1/TSC2), relieving its suppression of the small GTPase Rheb and thereby activating mTORRC1[53-55]. Negative regulation of this pathway is mediated by the tumor suppressor PTEN, which dephosphorylates PIP3 and limits AKT activation. Loss of PTEN function, commonly observed in breast cancer, results in constitutive activation of the PI3K/AKT/mTOR axis[56, 57].

mTOR signaling is also modulated by cellular energy status through AMP-activated protein kinase (AMPK), which inhibits mTORC1 activity under conditions of metabolic stress. This regulation ensures that anabolic processes are suppressed when energy levels are insufficient[58]. Additionally, mTORC1 exerts negative feedback on upstream signaling via S6K-mediated inhibition of insulin receptor substrate proteins, thereby creating a complex regulatory network with multiple feedback loops[59].

In breast cancer, aberrant activation of mTOR signaling contributes to multiple hallmarks of cancer, including enhanced proliferation, metabolic reprogramming, angiogenesis, and resistance to apoptosis. Hyperactivation of this pathway has been associated with poor prognosis and resistance to endocrine therapy and targeted agents[60-62]. Moreover, mTOR signaling plays a critical role in regulating tumor metabolism by promoting glycolysis, lipid synthesis, and mitochondrial function, thereby enabling tumor cells to adapt to fluctuating microenvironmnental conditions[63, 64].

Recent studies have further highlighted the role of mTOR signaling in therapeutic resistance, particularly in the context of targeted therapies. Inhibition of upstream pathways often leads to compensatory activation of mTOR signaling, underscoring its role as a central signaling hub in breast cancer[65]. Consequently, pharmacological inhibitors targeting mTOR, including rapalogs and ATP-competitive mTOR kinase inhibitors, have been developed and evaluated in clinical settings, although resistance mechanisms remain a major challenge[66, 67].

Collectively, these findings establish mTOR signaling as a critical regulator of breast cancer progression and a key node of integration for oncogenic signaling pathways, including its emerging crosstalk with BRCA1-mediated DNA repair mechanisms

Table 1: Functional Comparison of BRCA1 and mTOR in Breast Cancer[45-67]

Feature	BRCA1 Functions	mTOR Functions
Primary role	Tumor suppressor	Central regulator of cell growth
Core function	DNA damage repair (homologous recombination)	Protein synthesis and metabolism
Pathway type	DNA damage response (DDR)	PI3K/AKT/mTOR signaling
Genomic stability	Maintains genome integrity	Indirectly affects via metabolic control
Cell cycle regulation	Controls G1/S and G2/M checkpoints	Promotes cell cycle progression
Apoptosis	Promotes apoptosis upon severe DNA damage	Inhibits apoptosis (pro-survival)
Metabolism	Regulates oxidative stress and mitochondrial function	Controls glycolysis, lipid synthesis, and nutrient sensing
Mutation impact	Leads to genomic instability and cancer predisposition	Leads to uncontrolled growth and proliferation
Role in breast cancer	Frequently mutated in TNBC	Frequently hyperactivated
Therapeutic targeting	PARP inhibitors (synthetic lethality)	mTOR/PI3K/AKT inhibitors

4. BRCA1-mTOR Crosstalk in Breast Cancer

The interplay between BRCA1-mediated DNA damage response and mTOR-driven metabolic signaling represents a critical axis in breast cancer biology, integrating genomic instability with cellular growth and survival.

While these pathways were historically studied independently, recent evidence highlights a dynamic and bidirectional crosstalk that contributes to tumor progression and therapeutic resistance.

4.1 BRCA1 Loss Drives mTOR Activation

Loss of BRCA1 function is strongly associated with Hyperactivation of the PI3K/AKT/mTOR signaling pathways. Mechanistically, BRCA1 regulates PTEN stability and activity, and its deficiency results in PTEN loss, leading to increased PI3K signaling and sustained activation of AKT and mTOR[68-70]. Recent studies further demonstrate that BRCA1 deficiency induces metabolic reprogramming through activation of the PI3K/AKT/mTOR axis, promoting anabolic growth and survival advantages in breast cancer cells[89, 96].

In addition, emerging data indicate that DNA damage accumulation in BRCA1-deficient cells activates stress-responsive signaling pathways that converge on mTOR. Crosstalk between DNA damage sensor such as ATM/ATR and metabolic regulators further amplifies mTOR signaling under genomic stress conditions[71, 72, and 88]. This integration of genomic instability with metabolic signaling represents a key driver of tumor aggressiveness.

4.2 mTOR Regulates DNA Damage Response and BRCA1 Function

mTOR signaling plays a crucial role in modulating DNA repair processes by regulating protein translation and cellular metabolism. mTORC1-dependent translational control influences the synthesis of key DNA repair proteins. Thereby impacting homologous recombination efficiency[73, 74, and 93]. Recent findings suggest that mTOR signaling directly contributes to genome stability by coordinating DNA repair machinery and cellular energy status[93, 100].

Furthermore, mTORC2-mediated activation of AKT can negatively regulate components of the DNA damage response, potentially impairing BRCA1-mediated repair mechanisms[75, 76]. These findings highlight a bidirectional regulatory relationship in which mTOR signaling not only responds to genomic stress but also modulates BRCA1 functionality.

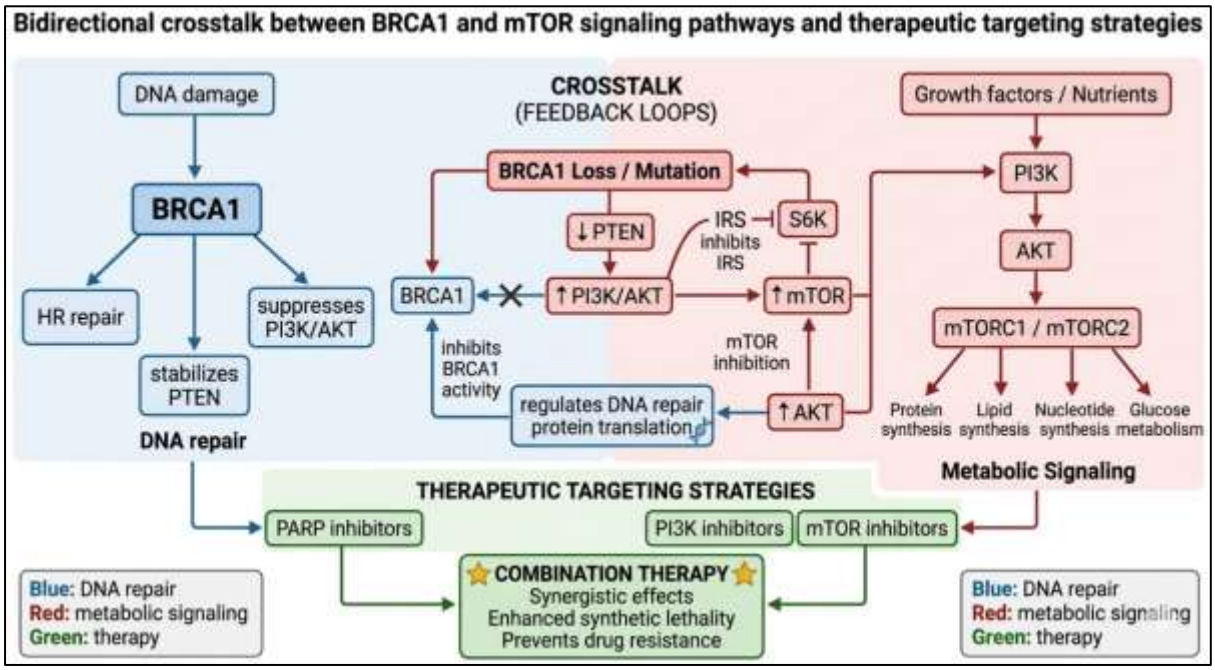


Figure 3: Bidirectional crosstalk between BRCA1 and mTOR signaling pathway and therapeutic targeted strategie

Schematic representation of the bidirectional interaction between BRCA1-mediated DNA damage response and PI3K/AKT/mTOR-driven metabolic signaling in breast cancer, highlighting key feedback loops and therapeutic interventions. On the left, DNA damage activates BRCA1, which promotes homologous recombination (HR)-mediated DNA repair, stabilizes PTEN, and suppresses PI3K/AKT signaling to maintain genomic integrity. On the right, growth factor and nutrient signaling activates PI3K, leading to sequential activation of AKT and mTOR complexes (mTORC1 and mTORC2), which regulate protein, lipid, and nucleotide synthesis as well as glucose metabolism. Central crosstalk mechanisms illustrate that BRCA1 loss or mutation reduces PTEN levels, resulting in enhanced PI3K/AKT signaling and mTOR activation, while AKT-mediated phosphorylation inhibits BRCA1 function, impairing DNA repair capacity. Additionally, mTOR signaling regulates the translation of DNA repair proteins, linking metabolic control to genome maintenance. Feedback loops are depicted, including S6K-mediated inhibition of insulin receptor substrate (IRS) proteins and mTORC2-dependent activation of AKT, which sustain pathway activation. The lower panel highlights therapeutic targeting strategies, including PARP inhibitors, PI3K inhibitors, and mTOR inhibitors, with combination therapy demonstrating synergistic effects, enhanced synthetic lethality, and the potential to overcome drug resistance. Color coding indicates DNA repair pathways (blue), metabolic signaling (red), and therapeutic interventions (green)[68-100].

4.3 Feedback Loops and Network Integration

The BRCA1-mTOR axis is tightly controlled by complex feedback loops that fine-tune signaling output. Activation of MTORC1 leads to phosphorylation of S6K, which supresses upstream signaling through inhibition of insulin receptor substrate proteins[77]. However, pharmacological inhibition of mTOR often results in compensatory activation of AKT, limiting therapeutic efficacy[78].

Recent studies have expanded this model by demonstrating that network-level adaptations, including metabolic rewiring and pathway redundancy, contribute to sustain signaling despite targeted inhibition[90, 91]. These adaptive responses underscore the importance of systems-level approaches to understanding BRCA1-mTOR crosstalk.

4.4 Therapeutic Implications of BRCA1-mTOR Crosstalk

The integration of BRCA1 and mTOR signaling pathways has important implications for therapeutic intervention. While BRCA1-deficient tumors are highly sensitive to PARP inhibitors, activation of the PI3K/AKT/mTOR pathway has been identified as a key mechanism of resistance[81, 82, and 98]. Consequently, combinational therapeutic strategies targeting both DNA repair and metabolic signaling pathways have gained significant attention.

Recent studies demonstrate that inhibition of PI3K or mTOR enhances the efficacy of PARP inhibitors by suppressing compensatory survival signaling and impairing DNA repair capacity[94, 95]. Moreover, targeting metabolic vulnerabilities in BRCA1-mutant tumors has emerged as a promising strategy to improve therapeutic outcomes[96].

Advances in multi-omics and systems biology have further enabled the identification of BRCA1-mTOR regulatory networks, facilitating the development of precision medicine approaches[100]. Additionally, next-generation therapeutic strategies targeting both pathways simultaneously are being actively explored in clinical settings[91, 99].

Table 2: Mechanisms of BRCA1–mTOR Crosstalk in Breast Cancer[94-99]

Mechanism	BRCA1 Role	mTOR Role	Outcome
PTEN regulation	Stabilizes and regulates PTEN	Activated when PTEN is lost	↑ PI3K/AKT/mTOR signaling
DNA damage signaling	Activates ATM/ATR pathways	Responds to stress signals	Coordinated DNA repair & survival
Metabolic reprogramming	Loss leads to altered metabolism	Drives anabolic metabolism	Tumor growth & survival
Protein synthesis control	Indirect regulation via repair pathways	Controls translation (mTORC1)	Impacts DNA repair protein levels
AKT feedback loop	BRCA1 loss enhances AKT activity	AKT activates mTOR	Sustained oncogenic signaling
AMPK interaction	Activated under stress	Inhibited by mTOR	Energy balance vs growth control
S6K-mediated feedback	No direct role	Inhibits IRS proteins	Negative feedback regulation
Therapy resistance	Mutation leads to PARP sensitivity	Activation leads to resistance	Reduced drug efficacy
Oxidative stress response	Regulates ROS detoxification	Promotes survival under stress	Enhanced tumor adaptability
Epigenetic regulation	Controls gene expression	Influences chromatin via metabolism	Tumor heterogeneity

5. Therapeutic Targeting of the BRCA1-mTOR Axis in Breast Cancer

The convergence of BRCA1-mediated DNA repair deficiency and Hyperactivation of the PI3K/AKT/mTOR pathway presents a compelling therapeutic opportunity in breast cancer. Targeting this axis enables simultaneous disruption of genomic maintenance and metabolic survival pathways, thereby enhancing treatment efficacy and overcoming resistance.

5.1 PARP Inhibitors and Synthetic Lethality

BRCA1-deficient tumors are highly sensitive to poly (ADP-ribose) polymerase (PARP) inhibitors due to synthetic lethality. Agents such as olaparib and talazoparib selectively induce cell death in homologous recombination-deficient tumors by accumulating unrepaired DNA damage. However, resistance mechanisms, including restoration of homologous recombination and activation of compensatory survival pathways such as PI3K/AKT/mTOR, limit long-term efficacy[101-104].

5.2 PI3K/AHT/mTOR Inhibitors

Targeting the PI3K/AKT/mTOR pathway has shown promise in breast cancer, particularly in tumors with pathway hyperactivation. mTOR inhibitors (rapalogs) such as everolimus have demonstrated clinical benefit, especially in hormone receptor-positive breast cancer. However, their efficacy is often limited by feedback activation of upstream signaling pathways, necessitating combination approaches[105-108].

5.3 Combination Therapies

Recent studies highlight the potential of combining PARP inhibitors with PI3K or mTOR inhibitors to enhance therapeutics response. PI3K inhibition has been shown to impair homologous recombination by downregulating BRCA1/2 expression, thereby sensitizing tumors to PARP inhibition. Similarly, mTOR inhibition can suppress compensatory survival signaling, enhancing the cytotoxic effects of DNA-damaging agents[109-112].

5.4 Overcoming Drug Resistance

Resistance to both PARP inhibitors and mTOR-targeted therapies remains a major clinical challenge. Mechanisms include secondary BRCA1 mutations, activation of alternative signaling pathways, and metabolic reprogramming. Dual-targeting strategies and the integration of immunotherapy are emerging as promising approaches to overcome resistance[113-116].

5.5 Clinical Translation and Ongoing Trails

Several clinical trials are currently evaluating combination therapies targeting the BRCA1-mTOR axis. Early-phase studies suggest improved progression-free survival with combination regimens, although toxicity and patient selection remain critical considerations[117-120].

Table 3: Therapeutic Strategies Targeting the BRCA1–mTOR Axis[117-120]

Drug/Class	Target	Mechanism of Action	Clinical Relevance in Breast Cancer
PARP inhibitors (Olaparib, Talazoparib)	PARP enzyme	Inhibit DNA repair → synthetic lethality	Effective in BRCA1-mutant cancers
PI3K inhibitors (Alpelisib)	PI3K	Blocks upstream signaling	Used in HR+ breast cancer
AKT inhibitors (Capivasertib)	AKT	Inhibits survival signaling	Under clinical investigation
mTOR inhibitors (Everolimus, Temsirolimus)	mTORC1	Inhibits protein synthesis & growth	Approved for HR+ breast cancer
Dual PI3K/mTOR inhibitors	PI3K + mTOR	Blocks entire signaling axis	Improved efficacy in resistant tumors
PARP + PI3K inhibitors	Dual targeting	Induces DNA damage + blocks survival	Overcomes resistance
PARP + mTOR inhibitors	Dual targeting	Enhances cytotoxicity	Promising in BRCA1-deficient tumors
Immunotherapy combinations	PD-1/PD-L1 + PARP/mTOR	Enhances immune response	Emerging strategy
Metabolic inhibitors	Glycolysis/lipid metabolism	Targets metabolic dependency	Experimental stage
Next-generation mTOR inhibitors	mTORC1/2	More complete pathway inhibition	Improved clinical outcomes (under study)

6. Emerging Areas and Future Directions

Emerging research on the BRCA1-mTOR axis is expanding beyond classical signaling paradigms, incorporating novel dimensions such as epigenetic regulation, tumor metabolism, immune modulation, and artificial intelligence-driven therapeutic strategies.

6.1 Epigenetic Regulation

Epigenetic modifications, including DNA methylation and histone acetylation, have been shown to regulate BRCA1 expression and mTOR pathway components. Dysregulation of these processes contributes to tumor heterogeneity and therapy resistance[121-123].

6.2 Metabolic Reprogramming

BRCA1 deficiency has been linked to altered cellular metabolism, including increased glycolysis and lipid synthesis, processes regulated by mTOR signaling. Targeting metabolic vulnerabilities represents a promising therapeutic avenue[124-126].

6.3 Tumor Microenvironment and Immunotherapy

The mTOR pathway plays a crucial role in immune cell regulation and tumor microenvironment modulation. Emerging evidence suggests that BRCA1-deficient tumors exhibit increased immunogenicity, providing a rationale for combining PARP inhibitors with immune checkpoint inhibitors[127-129].

6.4 AI and systems Biology Approaches

Advances in systems biology and artificial intelligence are enabling the integration of multi-omics data to better understand BRCA1-mTOR crosstalk. There approaches facilitate the identification of novel biomarkers and therapeutic targets[130-132].

6.5 Precision Oncology

The future of breast cancer therapy lies in precision medicine, where patients are stratified based on the molecular signature of BRCA1 and mTOR pathway alterations. Personalized therapeutic strategies are expected to improve clinical outcomes[133-135].

CONCLUSION

The BRCA1-mTOR signaling axis represents a critical interface linking genomic instability with metabolic reprogramming in breast cancer. BRCA1 deficiency not only impairs DNA repair but also promotes activation of the PI3K/AKT/mTOR pathway, driving tumor progression and therapeutic resistance. Emerging evidence highlights that targeting this crosstalk through combination strategies, particularly PARP and mTOR pathway inhibitors, offers a promising approach to enhance treatment efficacy. Future studies integrating multi-omics and precision oncology are expected to further refine therapeutic interventions and improve clinical outcomes.

Disclosure of Interest Statement

The author declares no conflict of interest.

Funding Statement

No funding was received for this work.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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