



# Emerging Therapeutic Targets in Triple-Negative Breast Cancer: Molecular Insights and Clinical Advances

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## DESCRIPTION

Triple-Negative Breast Cancer (TNBC) remains one of the most challenging forms of breast malignancy to address in clinical practice. Characterized by the absence of Estrogen Receptors (ER), Progesterone Receptors (PR), and Human Epidermal Growth Factor Receptor 2 (HER2), TNBC lacks the traditional targets that other subtypes of breast cancer depend on for treatment. Its aggressive biological behaviour, tendency for early relapse, and limited treatment options have driven intensive research efforts in recent years to identify new molecular avenues for therapeutic intervention.

With advancements in molecular profiling and genomic technologies, scientists have gained an improved understanding of the distinct features of TNBC at the cellular and genetic level. Unlike hormone receptor-positive cancers, TNBC is marked by considerable heterogeneity. This means that it cannot be approached as a single disease but rather as a spectrum of subtypes with differing molecular features. This complexity has necessitated the exploration of new molecular targets to design more focused treatment strategies.

One area of research has turned toward the DNA repair machinery within cancer cells. Many TNBC tumors display defects in DNA repair pathways, especially those associated with homologous recombination. This has led to increased interest in inhibitors targeting Poly (ADP-ribose) Polymerase (PARP), a key enzyme in the repair of single-strand DNA breaks. When cells already deficient in homologous recombination are exposed to PARP inhibitors, they accumulate DNA damage leading to cell death. Clinical trials have demonstrated meaningful responses in TNBC patients harboring BRCA1 or BRCA2 mutations, which impair homologous recombination, and several such drugs are now in clinical use or late-stage development.

Another focus involves targeting the immune system. TNBC often exhibits high levels of tumor-infiltrating lymphocytes and an immunogenic environment. These characteristics have made it a candidate for immunotherapies, particularly those targeting

immune checkpoints like PD-1 and PD-L1. By blocking these proteins, therapies aim to restore the immune system's ability to recognize and eliminate cancer cells. While response rates vary, some individuals have shown extended benefit from these approaches, especially when combined with chemotherapy.

Further exploration of cellular signaling pathways has led to the identification of the PI3K/AKT/mTOR axis as another relevant target in TNBC. Mutations and aberrant activation of this pathway have been observed in various subgroups of TNBC, contributing to tumor growth and survival. Inhibitors of AKT and mTOR are currently undergoing clinical testing, with some early studies suggesting additive effects when used in combination with conventional agents.

Additionally, the Androgen Receptor (AR), though traditionally associated with prostate cancer, is expressed in a subset of TNBCs. These tumors exhibit distinct molecular features and may respond to therapies that inhibit AR signaling. Several clinical trials are evaluating the role of anti-androgen drugs in managing AR-positive TNBC, adding a new layer to the treatment landscape.

The study of epigenetics has also brought new targets into focus. Histone Deacetylases (HDACs) and other epigenetic regulators control gene expression without altering the DNA sequence. Dysregulation in these pathways can drive tumor development and resistance to therapy. Efforts to modulate these processes through HDAC inhibitors and other compounds are underway, with early results suggesting potential in combination therapies.

Recent advances in Antibody-Drug Conjugates (ADCs) are being studied in the TNBC setting as well. These compounds combine a monoclonal antibody specific to a tumor antigen with a cytotoxic agent, allowing selective delivery of the drug to cancer cells while sparing healthy tissue. One such agent targeting Trop-2 has shown efficacy in trials and is being integrated into treatment regimens.

Despite the lack of conventional hormonal or HER2 targets, the research community has made strides in understanding the

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biology of TNBC and identifying vulnerabilities that can be exploited therapeutically. These efforts are slowly transforming a disease once seen as devoid of targeted options into one where multiple approaches are becoming available.

Continued investigation and clinical evaluation will be required to refine these strategies, determine optimal combinations, and identify which patients are most likely to benefit. Molecular

diagnostics and predictive biomarkers will play an increasingly vital role in this process, guiding decisions and improving outcomes. As our molecular understanding deepens, it opens possibilities for more effective and durable control of TNBC, offering new directions for those affected by this challenging condition.