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DNA methylation and immune evasion in triple-negative breast cancer: challenges and therapeutic opportunities

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Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer characterized by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Chemotherapy remains the primary treatment option, yet TNBC frequently develops resistance, leading to relapse and metastasis. Emerging evidence highlights the potential of combining DNA methylation inhibitors with immune checkpoint inhibitors (ICIs). DNA methylation contributes to immune escape by silencing immune-regulatory genes, thereby reducing the tumor's visibility to immune cells. Reversing this epigenetic modification can reinvigorate immune surveillance and enhance the efficacy of immunotherapies. This review discusses the role of DNA methylation in TNBC progression and immune evasion, focusing on recent advances in combination therapies involving DNA methylation inhibitors and ICIs. We discuss the underlying mechanisms that enable these therapeutic synergies, preclinical and clinical evidence supporting the approach, and the challenges posed by tumor heterogeneity, drug resistance, and toxicity. Finally, we explore the potential for personalized treatment strategies incorporating multi-omics data to optimize therapeutic outcomes. The integration of epigenetic therapies and immunotherapy offers a promising avenue for improving survival in TNBC patients.

KEYWORDS

triple-negative breast cancer, DNA methylation inhibitors, immune checkpoint inhibitors, immune evasion, epigenetic therapy, personalized medicine

Introduction

Breast cancer is a heterogeneous disease comprising several subtypes, with Triple-Negative Breast Cancer (TNBC) representing approximately 10-15% of all cases (1). Unlike other subtypes, TNBC lacks expression of ER, PR, and HER2 (2). The absence of these critical receptors makes TNBC non-responsive to hormone-based therapies and correlates with higher metastatic potential and shorter overall survival rates (3–6). TNBC tumors are often more prone to early metastasis, particularly to visceral organs, and show poor differentiation at the cellular level. The tumor microenvironment, including immune cells and stromal interactions, is crucial in driving TNBC's aggressiveness (7). TNBC is also associated with high genetic and phenotypic heterogeneity, complicating treatment efforts (8).

TNBC comprises multiple subtypes, including basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) subtypes. The BL2 subtype, enriched in growth factor signaling pathways, often exhibits stronger resistance to chemotherapy, whereas the BL1 subtype typically shows greater sensitivity to DNA-damaging agents (9). The LAR subtype is characterized by low immune cell infiltration and M2 macrophage activity, which are associated with poorer responses to immunotherapy and worse prognoses (10). In contrast, the BL1 and BL2 subtypes may benefit more from immunotherapy due to higher immune activation markers.

Chemotherapy remains the mainstay treatment for TNBC, but it is fraught with challenges. Despite being more sensitive to initial chemotherapy compared to other breast cancer subtypes, TNBC frequently develops resistance, leading to relapse and metastasis (8). Various molecular pathways often mediate this resistance, such as the overexpression of ATP-binding cassette (ABC) transporter proteins, which actively efflux chemotherapy drugs from cancer cells (11). The current standard of care for TNBC involves anthracycline and taxane-based chemotherapy regimens. While these therapies have demonstrated efficacy in early-stage disease, their effectiveness diminishes significantly in relapsed and metastatic cases due to the emergence of multi-drug resistance (2). Moreover, newer agents like immune checkpoint and PARP inhibitors have shown promise, but only a subset of patients respond favorably, leaving a substantial proportion with limited options (12). As a result, ongoing research is focused on identifying novel targets and combination therapies to overcome resistance and improve outcomes in TNBC patients.

Emergence of immunotherapy in cancer treatment

Cancer immunotherapy has rapidly expanded, revolutionizing treatment strategies across multiple malignancies. The main targets of these therapies are inhibitory receptors such as programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (13–15). These molecules play a crucial role in downregulating immune

responses, which tumors exploit to escape immune surveillance. Blocking these pathways has significantly improved outcomes for various cancers, including melanoma, non-small cell lung cancer, and renal cell carcinoma (16).

The first immune checkpoint inhibitors were approved for advanced-stage melanoma, showing long-lasting remissions in previously untreatable patients (17). PD-1 inhibitors such as nivolumab and pembrolizumab, as well as CTLA-4 inhibitor ipilimumab, have demonstrated durable responses across multiple cancer types by releasing the “brakes” on the immune system, allowing T cells to attack cancer cells more effectively. However, these treatments are not without challenges, as only a subset of patients exhibit favorable responses due to factors such as tumor mutation burden and the immunosuppressive tumor microenvironment (18).

Limited efficacy of immunotherapy as a monotherapy in TNBC

Despite the success of immune checkpoint inhibitors in other cancer types, their efficacy as monotherapy in TNBC has been limited. Although the introduction of ICIs targeting PD-1 and PD-L1 has shown promise, especially in combination with chemotherapy, the immune landscape of TNBC often presents substantial barriers to effective treatment (19, 20).

One major limitation is immune evasion. These include the recruitment of immunosuppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells, as well as upregulation of inhibitory receptors like TIM-3 and LAG-3, which reduce the efficacy of PD-1/PD-L1 blockade (19). TNBC often exhibits the characteristics of cold tumors, including a lack of tumor antigens, defects in antigen presentation, and insufficient T-cell infiltration in tumor tissues due to the failure of T cells to go home successfully. These mechanisms limit the effectiveness of ICIs (21). Moreover, MYC gene amplification is associated with the absence of immune cell infiltration, while mutations in the PI3K-AKT pathway may suppress the activation of innate immunity (22). To overcome these limitations, ongoing research explores combination therapies that include ICIs with chemotherapy, PARP inhibitors, and other immune-modulatory agents. These combinations aim to turn “cold” tumors into “hot” tumors, enhancing the immunogenicity of TNBC and improving patient outcomes (23, 24).

Epigenetic mechanisms and cancer progression

Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNA (ncRNA) regulation, are pivotal in cancer development and progression. DNA methylation typically occurs at CpG islands in the promoter regions of genes, silencing tumor suppressor genes in many cancers (25). Histone modifications, such as acetylation and methylation, regulate chromatin structure, influencing gene expression. The enzymes

involved in these modifications, such as histone deacetylases (HDACs) and histone methyltransferases, are often dysregulated in cancer, leading to aberrant transcriptional activation or repression (26). Non-coding RNAs, particularly microRNAs and long non-coding RNAs (lncRNAs), further modulate gene expression by affecting mRNA stability and translation (27). These epigenetic mechanisms are reversible, making them attractive targets for therapeutic intervention. Drugs targeting DNA methylation and histone modifications, such as DNA methyltransferase inhibitors (DNMTis) and HDAC inhibitors, are actively explored for cancer therapy, demonstrating promising results in hematologic and solid tumors (28).

Epigenetic modifications, particularly DNA methylation, are intimately involved in TNBC's immune evasion strategies. DNA methylation is a critical epigenetic mechanism that adds a methyl group to the cytosine ring within CpG islands, primarily in gene promoters. This process is catalyzed by DNA methyltransferases (DNMTs), such as DNMT1, DNMT3A, and DNMT3B, which play a crucial role in maintaining gene silencing (29, 30). Aberrant DNA methylation is prevalent in tumors, with variations in methylation levels across different regions exerting distinct impacts on gene transcription (Figure 1). Aberrant DNA methylation, particularly promoter hypermethylation, leads to the transcriptional repression of tumor suppressor genes, contributing to cancer initiation and progression (31). On the other hand, increased CpG site methylation within gene bodies can enhance gene expression, potentially by stabilizing the transcript (32). Blagitko-Dorfs (33) et al. discovered that the combined use of DNMT and HDAC

inhibitors can downregulate oncogenes such as MYC in acute myeloid leukemia cells through the demethylation of gene bodies. This demonstrates that targeting gene body demethylation may represent a viable epigenetic therapeutic strategy. DNA methylation can silence the expression of immune-related genes, including those involved in antigen presentation and interferon signaling pathways, which are critical for an effective immune response (34).

Interaction between DNA methylation and immune evasion

DNA demethylating agents have demonstrated therapeutic or diagnostic potential in hematological disorders (35), and in clinical trials involving patients with recurrent glioblastoma (36) and chemotherapy-resistant hepatocellular carcinoma (37). Furthermore, as reported by Linnekamp et al. (38), partial clinical responses have been observed in several solid tumors, including breast cancer, lung cancer, and colorectal cancer. These responses are characterized by gene demethylation and re-expression in certain patients. DNA methylation frequently silences immune-regulatory genes, impacting immune surveillance and evasion (39, 40). Hypermethylation leads to silencing tumor suppressor genes and immune-related genes, including those involved in antigen presentation and interferon signaling pathways (31). This silencing directly impacts immune escape mechanisms, as it reduces the expression of major histocompatibility complex (MHC) molecules and other immune-related markers, which are essential for effective

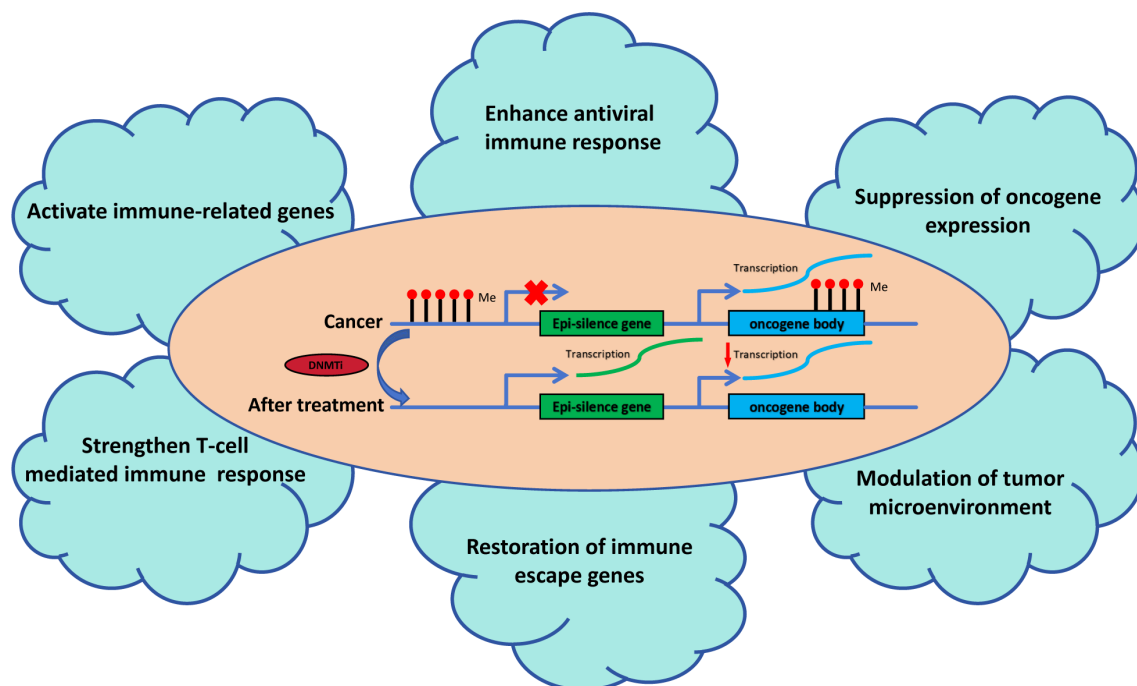


FIGURE 1

The role of DNA methyltransferase inhibitors in tumor immunity. DNMTis reactivate epi-silenced genes and suppress oncogene expression by reducing DNA methylation. This process enhances antiviral immune responses, activates immune-related genes, and strengthens T-cell-mediated immunity. It modulates the tumor microenvironment, restores immune escape genes, and suppresses oncogene-driven pathways, collectively improving tumor immune surveillance and therapeutic outcomes.

immune surveillance and response (41). Hypermethylation of immune-regulatory genes like PD-L1 reduces the tumor's ability to be recognized by cytotoxic T lymphocytes, promoting immune evasion and resistance to therapies (26). These findings suggest that targeting DNA methylation pathways could restore immune function and improve therapeutic outcomes in TNBC.

DNA methylation also plays a role in downregulating immune checkpoints, further enhancing immune evasion. The silencing of STING (stimulator of interferon genes), a crucial component of the innate immune response through DNA methylation, has been observed in TNBC. This silencing reduces the recruitment of immune cells to the tumor site, diminishing the anti-tumor immune response (42). Additionally, epigenetic modifications of immune-related genes contribute to the resistance in immunotherapy treatments, highlighting the potential of combining DNA methylation inhibitors with immunotherapy to overcome immune evasion (43).

Epigenetic modifications and the tumor microenvironment

Epigenetic modifications also influence the tumor microenvironment, enhancing tumor survival and resistance to therapy. TNBC's aggressive nature is partly due to the epigenetic remodeling of the extracellular matrix (ECM), which facilitates metastasis and therapeutic resistance (44). TNBC is notorious for its ability to evade the immune system by creating an immunosuppressive tumor microenvironment (TME) (45). One of the primary mechanisms involves the upregulation of immune checkpoint molecules such as PD-L1, which binds to PD-1 on T cells, effectively "turning off" the immune response and allowing the tumor to grow unchecked (46). This immune checkpoint blockade dampens cytotoxic T cell activity and enables TNBC cells to evade immune surveillance. TNBC tumors are also proficient at recruiting immunosuppressive cell populations, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), further suppressing the anti-tumor immune response (47, 48).

Tregs (CD4⁺Foxp3⁺) cells, play a crucial role in immune evasion by secreting immunosuppressive cytokines such as IL-10 and TGF- β . These cytokines inhibit the activity of cytotoxic T cells and natural killer cells, thereby protecting the tumor from immune-mediated destruction (46). Similarly, MDSCs are known to suppress T cell proliferation and cytokine production, facilitating the tumor's ability to escape immune detection (49). Together, these mechanisms create an immune-tolerant environment that allows TNBC to progress.

Clinical relevance

DNA methylation biomarkers hold significant prognostic value in TNBC. Studies show that aberrant DNA methylation patterns are associated with poor prognosis and resistance to conventional therapies, such as chemotherapy and immunotherapy (50, 51).

DNA methylation-induced silencing of tumor suppressor genes and immune-related genes contributes to chemotherapy resistance by preventing the reactivation of apoptotic pathways in cancer cells (52).

Moreover, DNA methylation has emerged as a mechanism of resistance to immunotherapies. Tumors with hypermethylated immune-regulatory genes often show reduced responsiveness to immune checkpoint inhibitors, which aim to enhance the body's immune response against cancer (53). Combining DNMT inhibitors with immunotherapies has demonstrated the potential to reverse resistance and improve outcomes in TNBC patients.

Combining DNA methylation with immunotherapy in TNBC

DNA methylation inhibitors, such as azacitidine and decitabine, are designed to reverse the epigenetic silencing of genes involved in immune regulation and tumor suppression. In the context of TNBC, these inhibitors can restore the expression of immune-related genes, enhancing the effectiveness of immunotherapies like ICIs (54). The hypermethylation of immune-related genes, particularly those involved in antigen presentation, limits immune cell infiltration and recognition, thus contributing to immune evasion in glioma (55). By reversing these epigenetic modifications, DNA methylation inhibitors promote immune activation, increasing tumor antigen visibility to cytotoxic T cells (56, 57). Preclinical studies have demonstrated the synergistic effects of combining DNA methylation inhibitors with ICIs in various cancers, including TNBC. For example, the combination of decitabine with anti-PD-1 therapy in mouse models of pancreatic cancer showed significantly improved survival rates, mediated by increased tumor-infiltrating lymphocytes and a reduction in immunosuppressive cell populations (58). Similar results have been observed in TNBC, where decitabine treatment increases the expression of antigen-presenting genes, such as MHC class I, leading to enhanced T cell-mediated immune responses (59). The underlying mechanisms of synergy between DNA methylation inhibitors and ICIs include enhanced immune cell infiltration, increased antigen presentation, and decreased levels of immunosuppressive factors within the TME. These effects are critical for converting immunologically "cold" tumors into "hot" tumors, which are more responsive to immune checkpoint blockade (53). Preclinical evidence suggests combining these therapies can induce durable anti-tumor responses, even in patients with advanced or resistant cancers.

Challenges and limitations of combination therapy

One of the most significant challenges in treating TNBC with combination therapies, is the intrinsic heterogeneity of TNBC tumors. This diversity leads to varying responses to treatments, as different subclones within a tumor may respond differently to the same therapy (60). Recent studies suggest that identifying TNBC subtypes with specific DNA methylation or immune-related gene

expression patterns may help personalize treatment strategies, improving the likelihood of therapeutic success (61). By classifying tumors into more homogeneous subgroups, therapies can be tailored to target the unique molecular features of each subtype, potentially overcoming the challenges posed by heterogeneity. Integrating large-scale multi-omics data requires addressing challenges such as computational demands, data standardization, and robust bioinformatics pipelines. From an ethical perspective, greater attention must be given to patient privacy, data security, and equitable access to personalized treatments derived from multi-omics data.

DNA methylation inhibitors face limitations in clinical application due to the broad spectrum of their target effects. Currently, these inhibitors are primarily used for refractory myelodysplastic syndromes and leukemia, where their therapeutic benefits have been clinically validated. However, the therapeutic efficacy remains unclear in solid tumors, as multiple genes may be epigenetically activated, complicating the treatment outcomes. DNA methylation inhibitors may also trigger compensatory or demethylation events that allow cancer cells to maintain their malignant phenotype despite treatment. Biomarkers such as PD-L1 expression, tumor mutational burden, and specific methylation patterns are being investigated to predict which patients will most likely benefit from these treatments (62).

The combination of DNA methylation inhibitors with immunotherapy introduces potential toxicity concerns, including immune-related adverse events (irAEs) and off-target effects. Immune checkpoint inhibitors can lead to autoimmune reactions, affecting organs such as the liver, lungs, and thyroid (38, 63). Similarly, DNA methylation inhibitors can cause off-target gene demethylation, potentially leading to unwanted gene expression changes that exacerbate toxicity. Studies have reported toxicities such as neutropenia, anemia, and elevated liver enzymes in patients receiving combination therapy.

Future prospects

Biomarkers such as DNA methylation signatures, immune cell infiltration profiles, and circulating tumor DNA (ctDNA) are emerging as potential tools for predicting response to combination therapies in TNBC. Recent advances in single-cell sequencing have enabled more precise characterization of tumor heterogeneity and immune cell interactions, leading to the discovery of novel biomarkers that may guide treatment decisions (64). These biomarkers can also help monitor treatment response and detect early signs of resistance, allowing for timely adjustments in therapy (65). Developing predictive biomarkers such as tumor-infiltrating lymphocyte (TIL) profiles and PD-L1 expression could improve patient selection for immunotherapy-based treatments, increasing the likelihood of therapeutic success (66).

There is growing interest in exploring other epigenetic therapies, such as histone deacetylase (HDAC) inhibitors. HDAC inhibitors can modulate gene expression, enhancing immune recognition of tumors and sensitizing cancer cells to immune checkpoint inhibitors (67). Dual targeting of epigenetic mechanisms, such as combining HDAC inhibitors with DNA methylation or immune checkpoint inhibitors, may lead to more robust anti-tumor responses in TNBC (13).

Preclinical studies have shown that HDAC inhibitors can enhance the infiltration of immune cells into tumors and promote the expression of tumor antigens, making them attractive candidates for combination therapies in TNBC (68).

Conclusion

The combination of DNA methylation and immune checkpoint inhibitors holds promise for enhancing the therapeutic efficacy of TNBC. By reversing the epigenetic silencing of immune-regulatory genes, tumor visibility to immune cells can be improved, potentially overcoming the immune evasion characteristic of TNBC. While preclinical and early clinical trials have provided encouraging results, challenges such as tumor heterogeneity, resistance, and toxicity must be addressed. Future research should focus on utilizing multi-omics integration techniques within combination therapy groups to explore the mechanisms of personalized treatment, thereby defining specific therapeutic strategies to improve patient outcomes.

Author contributions

W-YC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Validation, Writing – original draft. X-XC: Conceptualization, Data curation, Formal analysis, Validation, Writing – original draft. Y-RF: Data curation, Project administration, Validation, Writing – review & editing. RY: Data curation, Formal analysis, Project administration, Resources, Supervision, Writing – original draft. D-MS: Data curation, Project administration, Visualization, Writing – review & editing. DH: Formal analysis, Methodology, Supervision, Writing – review & editing. W-WZ: Data curation, Project administration, Visualization, Writing – review & editing. M-FX: Data curation, Project administration, Visualization, Writing – review & editing. X-XY: Conceptualization, Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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