THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 9

RESEARCH ARTICLE

SLFN12 and Triple Negative Breast Cancer: Unlocking New Possibilities in Chemotherapy Response

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OPEN ACCESS

PUBLISHED
30 September 2025

CITATION
Brown, SR., Author2, Z., et al., 2025. SLFN12 and Triple Negative Breast Cancer: Unlocking New Possibilities in Chemotherapy Response. Medical Research Archives, [online] 13(9). https://doi.org/10.18103/mra.v13i9.6947

DOI
https://doi.org/10.18103/mra.v13i9.6947

ISSN
2375-1924

ABSTRACT

In the rapidly evolving field of cancer pharmacology, biomarkers are a key to fulfilling the promise of precision medicine. While many candidates have shown early promise only to lose momentum, recent findings suggest that Schlafen family member 12 may represent a clinically meaningful advancement. Increased expression of Schlafen 12 has been linked to triple-negative breast cancer survival and sensitization to chemotherapeutic agents. Additionally, transcriptomic analyses has identified an eight-gene SLFN12 signature that has potential to predict treatment response – advancing its efficacy as a biomarker for triple-negative breast cancer. Taken together, using Schlafen 12 as a biomarker in triple-negative breast cancer may increase patient survival while simultaneously provide a method of precision oncology to a patient base with limited targeted treatment options.

Keywords: SLFN12, TNBC, Chemotherapy Sensitivity, Biomarkers, Precision Oncology

A High-Stakes Landscape: TNBC and the Urgent Need for Personalized Medicine

Breast cancer is more than just a statistic; it represents a reality that has affected countless lives. Therefore, exploration into its complexities highlights the urgent need for more effective solutions. Breast cancer is the most diagnosed cancer globally and stands as the second leading cause of cancer-related deaths among women[1]. Triple-negative breast cancer (TNBC) accounts for 10–15% of breast cancer diagnoses but contributes disproportionately to mortality. Increased rates of mortality are due to the lack of targetable receptors such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (ER, PR, HER2)[1,2]. Due to the absence of receptor-targeted therapies, TNBC patients often depend on non-specific chemotherapy and radiation treatments, with no predictive biomarkers for response. This disparity has left a significant gap between diagnosis and optimized care for these patients – highlighting the immense need for a more personalized approach to treatment.

Recently published research has indicated that the Schlafen (SLFN) protein family plays various roles in cancer biology and influences patient survival. SLFN12—a member of the Schlafen gene family—has emerged as a key regulator of tumor biology in TNBC by influencing cell differentiation, proliferation, and response to treatment[2-4]. SLFN12 expression is associated with reduced tumor aggressiveness, likely due to its role in prompting epithelial differentiation and impairing DNA repair pathways[4]. Functionally, SLFN12 enhances chemosensitivity to agents such as carboplatin and paclitaxel by reducing CHK1/2 phosphorylation, thus limiting the cell's ability to repair DNA damage[5].

Compared to traditional breast cancer biomarkers such as BRCA1/2 or Ki-67, SLFN12 offers a more dynamic transcriptomic readout that reflects functional treatment susceptibility rather than static genetic mutations. Importantly, it also shows differential expression across racial groups, with notable disparities between African American and Caucasian patients[3,4]. This makes SLFN12 uniquely positioned to inform both personalized therapy and efforts to address racial inequalities in TNBC outcomes.

SLFN12: A Biomarker Worth Watching

SLFN12 distinguishes itself as a promising biomarker in TNBC due to its multifaceted role in prognosis, tumor biology, and therapeutic response. Elevated SLFN12 mRNA levels have been shown to positively correlate with overall survival in TNBC patients, supporting its utility for risk stratification and informing treatment strategies[3]. This prognostic relevance is particularly significant given the lack of targeted treatment options available for TNBC patients. Functionally, SLFN12 overexpression has been demonstrated to suppress tumor growth and promote cellular differentiation in vitro, suggesting it may facilitate a phenotypic shift from aggressive to more treatable tumor states[4].

Compared to traditional breast cancer biomarkers such as BRCA1/2 or Ki-67, SLFN12 offers a more dynamic transcriptomic readout that reflects functional treatment susceptibility rather than static genetic mutations. Importantly, it also shows differential expression across racial groups, with notable disparities between African American and Caucasian patients[3,4]. This makes SLFN12 uniquely positioned to inform both personalized therapy and efforts to address racial inequalities in TNBC outcomes.

Furthermore, SLFN12 has been shown to enhance TNBC cell sensitivity to chemotherapeutic agents such as carboplatin, paclitaxel, and camptothecin, as well as to zoledronic acid, a bisphosphonate with potential anti-tumor activity—an effect mechanistically linked to decreased CHK1/2 phosphorylation, which impairs DNA damage repair and improves cytotoxic efficacy[5]. SLFN12 causes differential expression of eight significant cancer genes (CALB2, EEF1A2, NQO1, FBP1, UCA1, PAEP, GJB3, and GJA1)[3]. PAEP, GJA1, EEF1A2, and NQO1 were downregulated following SLFN12 overexpression whereas UCA1, FBP1, CALB2, and GJB3 were each upregulated – allowing for establishment of a gene signature[3]. Gene signatures can be used to identify biomarkers for disease diagnosis and prognosis - as well as to predict response to therapies by looking at levels of specific genes associated with a particular protein, in this instance SLFN12. Following chemotherapy treatment in SLFN12-overexpressing TNBC cells, the eight SLFN12 signature cancer genes resulted in differential responses in mRNA expression[3]. Understanding SLFN12 signature gene patterns before and after chemotherapy is essential for understanding personalized chemotherapy treatments for TNBC patients and developing SLFN12 as a TNBC biomarker.

Future Directions: Advancing SLFN12 Toward Clinical Application in TNBC

Before SLFN12 transitions from a promising preclinical biomarker into a clinically actionable tool for the treatment of TNBC, several key steps are needed. First, its prognostic and predictive utility must be validated in prospective, racially diverse TNBC cohorts to ensure broad applicability and address known disparities in outcomes[6,9]. Integrating SLFN12 expression into multi-omic datasets will be essential to uncover its interactions within broader regulatory networks and identify synergistic therapeutic targets[3,7].

Additionally, pharmacologic strategies must be explored to upregulate SLFN12 expression, potentially enhancing treatment response in low-expressing tumors. Currently, interferon alpha (IFN-α2) is the only known stimulator of SLFN12[3,4].

Emerging studies suggest that SLFN12 may also play a role in modulating the tumor immune microenvironment. While the precise mechanisms remain under investigation, transcriptomic analyses have linked SLFN12 to genes involved in immune regulation and inflammation, suggesting broader relevance beyond chemosensitivity[3,7]. Notably, research in glioma has demonstrated that elevated SLFN12 expression is associated with reduced response to PD-1 inhibitors, highlighting a potential role in predicting immunotherapy

outcomes[8,10]. Future clinical trials should take into consideration using SLFN12 as a stratification tool in adaptive trial designs. This would enable dynamic treatment modification based on an up-and-coming real-time biomarker.

Finally, the development of AI-informed models that incorporate SLFN12 alongside other molecular and clinical variables may support more precise, patient-specific treatment planning—advancing the goal of individualized cancer care.

Conclusion

SLFN12 is more than a gene—it may act as a cornerstone of next-generation TNBC treatment, offering insights into prognosis, chemosensitivity, and health disparity mitigation. These findings are not only relevant to breast cancer pharmacology, but extend to immunotherapy design, biomarker-informed precision oncology, and inclusive clinical trial strategies. For oncologists, pharmacologists, and molecular biologists alike, SLFN12 holds significant potential for discovery, innovation, and impact.

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