

Invasive Ductal Carcinoma of the Breast: Molecular Evolution, Immune Escape, and Therapeutic Implications

NKIRUKA ROSE UKIBE¹, CHARLES CHINEDUM ONYENЕКWE², CHIDIOGOR MARIGOLD
IHEUKWUMERE³, CHINONSO COLIN NWABUEZE⁴

^{1,4}*Department of Immunology and Immunochemistry, Faculty of Medical Laboratory Science,
Nnamdi Azikiwe University, Awka, Nigeria*

^{2,3}*Department of Applied Microbiology, Faculty of Biosciences, Nnamdi Azikiwe University, Awka,
Nigeria*

Abstract- *Invasive ductal carcinoma (IDC) is the most common histological form of breast cancer and is characterized by marked molecular and immunological heterogeneity. Its progression from ductal carcinoma in situ (DCIS) to invasive disease is accompanied by disruption of the myoepithelial and basement-membrane barriers, extracellular-matrix remodelling, genomic evolution and changes in the tumour microenvironment (TME). Cancer immunoediting provides a useful framework for understanding this progression through elimination, equilibrium and escape. During escape, tumour cells and associated stromal and immune populations can reduce effective antitumour immunity through altered antigen presentation, immune-checkpoint signalling, immunosuppressive cytokines, metabolic reprogramming and recruitment of regulatory immune cells. Evidence from breast tumours demonstrates reduced cytotoxic T-cell activity and changes in immune-cell composition during the transition from DCIS to IDC. Genomic alterations involving TP53, PIK3CA and GATA3 contribute to subtype-specific tumour behaviour, while emerging studies implicate metabolic regulators such as acyl-CoA thioesterase 7 (ACOT7) in IDC biology and immune contexture. PD-L1 assessment illustrates the translational challenge of converting tumour immunobiology into reliable clinical biomarkers because assay platforms, scoring systems and specimen characteristics can influence classification. Therapeutically, immune-checkpoint blockade has become clinically important in selected breast-cancer populations, particularly early-stage triple-negative disease, while antibody–drug conjugates have expanded treatment options for HER2-low advanced breast cancer. This review synthesizes the immunological and molecular mechanisms underlying IDC progression, highlights diagnostic and therapeutic implications, and identifies research priorities relevant to resource-constrained settings.*

Keywords: *invasive ductal carcinoma; tumour microenvironment; immune escape; immunoediting;*

triple-negative breast cancer; immunotherapy; biomarkers.

I. INTRODUCTION

Breast cancer is a biologically heterogeneous disease in which malignant epithelial cells interact continuously with immune, stromal and vascular components. IDC represents the most common histological subtype and encompasses tumours with markedly different receptor profiles, genomic alterations, immune characteristics and treatment responses. Its biological behaviour therefore cannot be explained by tumour-cell proliferation alone; it reflects interactions between evolving malignant clones and the surrounding TME.

Cancer immunoediting provides a conceptual framework for these interactions. It describes three overlapping phases: elimination, equilibrium and escape. In the elimination phase, innate and adaptive immune responses can recognize and destroy transformed cells. During equilibrium, immune pressure restrains tumour growth while selecting for cellular variants capable of surviving immune attack. In the escape phase, selected tumour populations acquire or exploit mechanisms that reduce immune recognition and effector function, permitting clinically apparent progression.[1,2]

In breast cancer, immune escape is particularly relevant during progression from DCIS to IDC. Studies comparing normal breast tissue, DCIS and IDC demonstrate changes in leukocyte composition, reduced CD8⁺ T-cell signatures and fewer activated GZMB⁺ CD8⁺ T cells in IDC, supporting the concept

that immune and tumour compartments co-evolve during invasion.[3,4]

II. FROM DCIS TO IDC: STRUCTURAL AND IMMUNE EVOLUTION

DCIS is characterized by malignant epithelial proliferation confined within the ductal system, whereas IDC is defined by invasion through the basement membrane into the surrounding stroma. The transition is associated with loss or disruption of the normal myoepithelial barrier and extracellular-matrix remodelling. Matrix metalloproteinases and other proteolytic systems contribute to extracellular-matrix degradation, while epithelial–mesenchymal plasticity can enhance cellular motility and invasion.

The transition is also immunologically important. In DCIS, immune cells may be concentrated around areas of myoepithelial disruption, while invasive tumours show more direct interaction between malignant cells and infiltrating leukocytes. A detailed analysis of normal tissue, DCIS and IDC found reduced activated CD8⁺ T-cell signatures in IDC and differences in T-cell receptor clonotype diversity between in situ and invasive lesions. High PD-L1 expression and CD274 amplification were particularly observed in triple-negative IDC.[3]

These findings support a model in which invasion is not simply the physical crossing of an anatomical boundary. Instead, it occurs in the context of reciprocal tumour–stroma–immune interactions that can favour tumour survival and progression.

III. MOLECULAR AND GENOMIC LANDSCAPE OF IDC

IDC contains recurrent alterations in signalling and tumour-suppressor pathways, although their frequencies vary by molecular subtype. TP53, PIK3CA and GATA3 are among the best-recognized recurrently altered genes in breast cancer. TP53 disruption can impair DNA-damage responses, cell-cycle control and apoptosis, whereas activating PIK3CA alterations can increase PI3K–AKT–mTOR signalling and promote survival and proliferation. GATA3 alterations are particularly relevant to luminal

differentiation and may define distinct evolutionary pathways.[5–7]

These alterations should not be interpreted as isolated events. Genomic instability, oncogenic signalling and immune selection interact during tumour evolution. Changes that increase proliferation or survival may also alter antigenicity, cytokine production, immune-cell recruitment or sensitivity to therapy. The result is a dynamic population of tumour subclones rather than a genetically uniform lesion.

IV. CANCER IMMUNOEDITING AND IMMUNE ESCAPE IN IDC

During immune escape, tumour cells can reduce effective immune surveillance through several complementary mechanisms. These include reduced antigen presentation, expression of inhibitory ligands such as PD-L1, secretion of immunosuppressive mediators, alteration of metabolic conditions within the TME and recruitment or polarization of suppressive immune and stromal populations.[1,2,4] PD-1/PD-L1 signalling is one of the most clinically developed mechanisms. PD-L1 expressed by tumour or immune cells can engage PD-1 on activated T cells and contribute to functional exhaustion. However, PD-L1 is only one component of a broader network involving regulatory T cells, tumour-associated macrophages, cancer-associated fibroblasts, myeloid-derived suppressor cells and soluble mediators such as TGF- β and IL-10.[4,8]

The TME can therefore be considered an active participant in IDC progression. Tumour-associated macrophages may support angiogenesis, matrix remodelling and immunosuppression. Cancer-associated fibroblasts can modify extracellular matrix architecture and influence immune-cell trafficking. Regulatory T cells and other suppressive populations can further reduce effective cytotoxic responses. Their relative contribution differs among molecular subtypes, tumour stages and individual patients.[8,9]

V. METABOLIC AND EMERGING MOLECULAR MECHANISMS

5.1 ACOT7 and metabolic regulation

An emerging area of IDC research is the relationship between tumour metabolism and immune function. ACOT7 is an acyl-CoA thioesterase involved in lipid metabolism. A 2026 multi-omics study reported increased ACOT7 expression in IDC compared with non-malignant tissue and found associations between higher expression, adverse clinical outcomes and differences in immune-cell infiltration. The study also linked ACOT7-related expression patterns to fatty-acid metabolism and PPAR-associated pathways.[10] These findings are important but should be interpreted appropriately. Current evidence supports ACOT7 as an emerging biomarker and candidate regulator of IDC biology; it does not yet establish ACOT7 as a validated therapeutic target or prove a direct causal pathway between ACOT7 activity and T-cell exhaustion in patients. Further functional and clinical studies are required.

5.2 cGAS–STING, non-coding RNA and immune regulation

DNA damage and cytosolic DNA sensing are increasingly recognized as components of tumour–immune interaction. The cGAS–STING pathway can detect cytosolic DNA and promote type I interferon signalling, thereby contributing to antitumour immunity. However, cancers can alter DNA-sensing and downstream inflammatory pathways, potentially converting or attenuating immune-stimulatory signals. Non-coding RNAs are among the emerging regulators of these processes.

The original seminar highlighted FAM83H-AS1 as a specific regulator of cGAS–STING signalling in aggressive breast cancer. Because the precise mechanism requires a stronger primary peer-reviewed source before publication, this review treats it as an emerging research area rather than an established clinical pathway.

VI. TUMOUR MICROENVIRONMENT AND IMMUNE DYSFUNCTION

The IDC TME contains malignant epithelial cells together with fibroblasts, endothelial cells, macrophages, lymphocytes and extracellular-matrix components. The balance among these populations

influences invasion, angiogenesis, immune surveillance and treatment response.

Immune infiltration is not uniformly favourable or unfavourable. Its biological significance depends on the phenotype, location and functional state of infiltrating cells as well as tumour subtype. Cytotoxic lymphocytes and natural killer cells can mediate tumour-cell killing, whereas regulatory T cells, suppressive myeloid populations and certain macrophage states may promote immune tolerance. In breast cancer, immune contexture is also associated with response to chemotherapy and targeted therapy, particularly in HER2-positive and triple-negative disease.[3,8,9]

This heterogeneity has practical implications for biomarker development. A single circulating or tissue marker is unlikely to capture the complete immune state of an IDC. Multiparametric approaches combining tumour phenotype, immune markers and clinical characteristics may therefore provide more informative biological stratification.

VII. PD-L1 AS A DIAGNOSTIC AND THERAPEUTIC BIOMARKER

PD-L1 testing illustrates the challenges of translating immunobiology into routine laboratory diagnostics. Clinically used assays differ in antibody clone, platform, scoring system and intended therapeutic indication. Depending on the assay, PD-L1 may be evaluated in tumour cells, immune cells or by a combined positive score (CPS).

Comparative studies in TNBC have demonstrated that SP142, SP263 and 22C3 do not produce identical classifications. In the IMpassion130 biomarker population, SP142 identified fewer PD-L1-positive cases than SP263 or 22C3 at the same immune-cell threshold, and analytical concordance was incomplete.[11] Other studies similarly show that assay and scoring method affect PD-L1 classification.[12,13] Consequently, PD-L1 results should be interpreted according to the assay-specific clinical indication rather than treating all PD-L1 tests as interchangeable.

This issue is particularly relevant in resource-constrained laboratories, where tissue fixation, cold-ischaemia time, assay availability, quality control and specialist interpretation may influence test performance. Strengthening pre-analytical standardization, quality assurance and laboratory–pathology collaboration is therefore essential for reliable biomarker-guided treatment.

VIII. THERAPEUTIC IMPLICATIONS

Improved understanding of immune escape has contributed to the development of immune-checkpoint inhibitors and biomarker-directed treatment strategies. The clinical relevance is strongest in selected breast-cancer populations rather than across all IDC.

8.1 Immune-checkpoint blockade in TNBC

KEYNOTE-522 established an important role for pembrolizumab combined with neoadjuvant chemotherapy followed by adjuvant pembrolizumab in high-risk early-stage TNBC. In the final overall-survival analysis, 60-month overall survival was 86.6% with the pembrolizumab regimen compared with 81.7% with chemotherapy plus placebo.[14] These results support the importance of immune-checkpoint blockade in appropriately selected early-stage TNBC.

8.2 HER2-low disease and antibody–drug conjugates

Therapeutic development has also challenged the traditional binary interpretation of HER2 status. In DESTINY-Breast04, trastuzumab deruxtecan improved progression-free and overall survival compared with physician's-choice chemotherapy in patients with previously treated HER2-low metastatic breast cancer.[15] The trial illustrates how quantitative differences in target expression can have therapeutic implications and reinforces the importance of accurate pathology and biomarker classification.

8.3 Emerging precision approaches

Other approaches under investigation include circulating tumour DNA, molecular monitoring of treatment resistance, combination immunotherapy, antibody–drug conjugates and strategies directed at tumour metabolism or the TME. These approaches remain heterogeneous in maturity and should be

distinguished from treatments supported by established phase III clinical evidence.

IX. RELEVANCE TO RESOURCE-CONSTRAINED SETTINGS

In many low- and middle-income settings, the biological complexity of IDC is compounded by limitations in screening, pathology capacity, molecular testing, treatment access and continuity of care. These constraints can delay diagnosis and limit access to biomarker-directed therapies.

Laboratory medicine has a central role in addressing these gaps. Priority areas include reliable histopathology and immunohistochemistry, external quality assessment, standardized tissue handling, validated biomarker assays, appropriate molecular testing where available, and development of affordable approaches that can be implemented locally. Research from African populations is also needed to ensure that biomarker evidence reflects populations that may differ in disease presentation, genetic background and healthcare access.

X. RESEARCH GAPS AND FUTURE DIRECTIONS

Clarify the molecular events that distinguish DCIS lesions that remain in situ from those that progress to invasive disease.

Integrate genomic, transcriptomic, metabolic and immune measurements to define biologically meaningful IDC subgroups.

Validate emerging biomarkers such as ACOT7 in independent clinical cohorts and determine whether observed associations are causal or correlative.

Improve harmonization of PD-L1 testing by linking assay-specific measurements to the therapeutic indication for which the test is intended.

Develop affordable biomarker panels suitable for laboratories in low- and middle-income settings.

Generate prospective African datasets incorporating clinicopathological, molecular and immune variables. Evaluate how treatment exposure alters the tumour and systemic immune environment, ideally using longitudinal sampling.

Strengthen translational research connecting circulating biomarkers with tissue phenotype and clinically relevant outcomes.

XI. CONCLUSION

IDC is a dynamic disease in which tumour evolution, genomic alteration and immune regulation interact throughout progression. The transition from DCIS to invasive disease is accompanied by changes in the myoepithelial barrier, extracellular matrix, immune-cell composition and tumour-cell phenotype. Cancer immunoediting provides a useful framework for understanding how immune pressure can both restrain tumour growth and select for immune-resistant clones. Immune escape in IDC is multifactorial, involving checkpoint signalling, suppressive immune and stromal populations, altered metabolism and molecular changes that influence tumour-immune communication. PD-L1 testing demonstrates the practical challenge of translating this biology into reproducible clinical biomarkers, while recent clinical trials show that appropriately selected patients can benefit from immune-checkpoint blockade and novel antibody-drug conjugates. Future progress will depend on integrated biomarker strategies, rigorous assay validation and research that reflects the populations and healthcare realities of resource-constrained settings.

Declarations

Author Contributions

Conceptualization: Nkiruka R. Ukibe.
Literature Review: Nkiruka R. Ukibe and Chinonso C. Nwabueze.

Manuscript Development and Drafting: Nkiruka R. Ukibe and Chinonso C. Nwabueze.
Critical Review and Revision: Nkiruka R. Ukibe, Charles C. Onyenekwe, and Chidiogor M. Iheukwumere.

Academic Supervision: Nkiruka R. Ukibe.
Final Approval of the Manuscript: All authors.

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Conflicts of Interest

“The authors declare no conflicts of interest.”

REFERENCES

- [1] Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases—elimination, equilibrium and escape. *Curr Opin Immunol*. 2014;27:16–25. [ScienceDirect](#).
- [2] Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science*. 2011;331:1565–1570. [Science](#).
- [3] Gil Del Alcazar CR, Huh SJ, Ekram MB, et al. Immune escape in breast cancer during in situ to invasive carcinoma transition. *Cancer Discov*. 2017;7(10):1098–1115. [AACR](#).
- [4] Gil Del Alcazar CR, Alečković M, Polyak K. Immune escape during breast tumor progression. *Cancer Immunol Res*. 2020;8(4):422–427. [AACR](#).
- [5] Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature*. 2012;490:61–70. [Nature](#).
- [6] Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature*. 2012;486:346–352. [Nature](#).
- [7] Nik-Zainal S, Davies H, Staaf J, et al. Landscape of somatic mutations in 560 breast cancer whole-genome sequences. *Nature*. 2016;551:47–55.
- [8] Steven A, Seliger B. The role of immune escape and immune cell infiltration in breast cancer. *Breast Care (Basel)*. 2018;13:16–21. [Karger](#).
- [9] Domschke C, Schneeweiss A, Stefanovic S, et al. Cellular immune responses and immune escape mechanisms in breast cancer: determinants of immunotherapy. *Breast Care (Basel)*. 2016;11:206–212.

- [10] Song CS, Quan Y, Shan Y, et al. Prognostic significance and regulatory role of ACOT7 in the tumor immune microenvironment of breast invasive ductal carcinoma: a multi-omics analysis. *Front Immunol.* 2026;17:1735908. [Frontiers](#).
- [11] Rugo HS, Loi S, Cortes J, et al. PD-L1 immunohistochemistry assay comparison in atezolizumab plus nab-paclitaxel-treated advanced triple-negative breast cancer. *J Clin Oncol.* 2021;39:2679–2689.
- [12] Lee SE, Park HY, Lim SD, et al. Concordance of programmed death-ligand 1 expression between SP142 and 22C3/SP263 assays in triple-negative breast cancer. *J Breast Cancer.* 2020;23:303–313. [Journal of Breast Cancer](#).
- [13] Noske A, Wagner DC, Schwamborn K, Foersch S, Steiger K, Kiechle M, et al. Interassay and interobserver comparability study of four programmed death-ligand 1 (PD-L1) immunohistochemistry assays in triple-negative breast cancer. *Breast.* 2021;60:238–244. [ScienceDirect](#).
- [14] Schmid P, Cortes J, Dent R, et al. Overall survival with pembrolizumab in early-stage triple-negative breast cancer. *N Engl J Med.* 2024;391:1981–1991. [New England Journal of Medicine](#).
- [15] Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Engl J Med.* 2022;387:9–20. [New England Journal of Medicine](#).