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Review Article

Pathology Section

Recent Advances in Therapeutic Management of Invasive Ductal Carcinoma: A Narrative Review

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ABSTRACT

Invasive Ductal Carcinoma (IDC), a frequently reported subtype of Breast Cancer (BC), is affected by complex pathogenic processes, including Hormone Receptors (HR) signaling and growth factors. For initiation and development of IDC, deregulating Oestrogen Receptor (ER) signaling pathways plays a critical role by affecting cell growth, variation, and survival. Moreover, diverse Progesterone Receptor (PR) signaling mechanism modified ER-driven transcription factors, leading to endocrine resistance. Interestingly, tumour signaling mechanisms are strengthened by interaction between ER or PR and human Epidermal Growth Factor Receptor 2 (HER2/neu). Over-expression of HER2 allows proliferation via Protein Kinase B or Phosphoinositide3-kinase, and Mitogen-Activated Protein Kinase (MAPK) pathways, thereby leading to ER-independent mechanisms as well as resistance to Endocrine Therapy (ET). Emergent multi-omics interventions including single-cell and next-generation sequencing, and mass-spectrometry imaging, have unraveled molecular heterogeneity in IDC, thereby offering insights into Ductal Carcinoma In Situ (DCIS) progression to IDC and facilitate novel biomarker identification treatment prognostication. In a similar context, advancements of targeted therapies, including dual HER2 inhibition, antibody-drug conjugates, and combination treatments with endocrine agents, have enhanced personalised treatment strategies, although needs further clinical investigation. Thus, the present review aims to elucidate the role of molecular diagnostics and targeted therapeutics in IDC management, integrating existing literature to improve clinical management in IDC and tailored future research.

Keywords: Biomarker, Endocrine resistance, HER2/neu Pathway, Oestrogen receptor

INTRODUCTION

The BC, diagnosed frequently among women aged >30 years, constituted nearly 32% of overall new cancer cases annually. In 2025, an estimated 316,950 new cases of BC and 59,080 cases of DCIS annually in the United States have been reported [1]. Primary histological subtypes of Invasive Breast Cancer (IBC) include invasive lobular carcinoma and IDC accounting for nearly 80% of cases in women and 85% in men [2,3]. IDC complicates histological categorisation by exhibiting significant variations among clinical, morphological, and genomic profiles [2,3].

The IDC represents various histological features including nests, diffused sheets, single cellular infiltration, and cords depending on the existence or absence of tubular variation [4]. The structural diversity illustrates structural complexities that regulate oncogenic profiles and response to treatment. Overall, depicting molecular biomarkers with therapeutic and predictive values are essential for meticulous tumour progression and treatment optimisation.

The Epidermal Growth Factor Receptors (EGFR) or ErbB family including HER1, HER2, HER3, and HER4 play a prominent role in regulating cellular progression, variation and survival. HER2 is overexpressed in nearly15% to 30% of invasive BCs and function as a major prognostic marker, specifically in IDC management [5]. Furthermore, HRs such as ERs and PRs functions as vital biomarkers relevant to enhanced treatment response to ETs including, tamoxifen impeding receptor-mediated signaling pathways [2]. Conversely, HR-negative tumours, specifically triple-negative BCs facilitate increased aggressiveness with deficient targeted treatment alterations [6].

With advanced high-throughput molecular profiling techniques, IDC has been distinguished according to the status of receptors and downstream processes, thus, enhancing the tumour microenvironment comprehensively and metastatic performance [7,8]. Despite significant advancements in medical oncology, the complex relationship between IDC and targeted therapies remains unexplored, necessitating further investigation [5,6]. Thus, the present review aimed to critically explore the existing studies on hormone and growth factor receptor-driven signaling processes involved in IDC and synthesise current inferences that elucidate the generation and optimisation of targeted therapeutic strategies.

Methodology

Literature review included electronic databases such as PubMed, Google Scholar, Scopus, and DOAJ. The search was restricted to studies published in English language from January 2001 to March 2025. The literature review was focused on pathological pathways of IDC and therapeutic agents acting on this pathway. Studies that were consistent with the objectives of the present review, including pathogenic mechanisms, HRs, biomarkers and clinical implications involved in IDC management were identified, critically appraised, and synthesised in a comprehensive format.

Pathogenic Mechanisms and Hormone Receptors (HR) Involved in IDC Development

The IDC pathogenesis encompasses intricate processes among genetic, epigenetic, and micro environmental factors driving tumour initiation and development [7]. Divergent Fibroblast Growth Factor (FGF) receptors demonstrate substantial mechanisms that are usually linked to reduced expression of steroid HR, especially PR, thus resulting in tumour phenotypes that are both aggressive as well as hormone-independent. This type of receptor interaction boosts proliferation and anti-apoptotic signaling, ultimately leading to resistance to ET [9].

Epigenetic deregulation, including histone modification and DNA methylation, results in transcription silencing of tumour suppressor genes and oncogenic activation, particularly during transition to invasive disease from DCIS and Atypical Ductal Hyperplasia (ADH) [10]. In similar manner, Hedgehog pathway enables Epithelial-to-

Mesenchymal Transition (EMT) and reduces cellular adhesion, thereby stimulating invasion [11]. Moreover, proteomic analyses affects modification of protein that governs adhesion, metabolism, and apoptosis, thus highlighting molecular complexity of IDC [7].

Key hormone and growth factor receptors, including ER, PR, and HER2, involved in IDC activate molecular mechanisms essential for mammary gland development, but become appropriated during tumour development [12]. Mutations activating proto-oncogenes and tumour suppressor deficiency dysregulate checkpoints controlling proliferation, survival, and differentiation [Table/Fig-1] [13]. In combination, such mechanisms develop IDC as a heterogenous malignancy featured by therapy resistance and stem cell-driven progression [12].

Oestrogen Receptor (ER) and Progesterone Receptor (PR) Signaling Pathway

Nearly one-third of women with ER-positive BC eventually develop resistance to ER-targeted therapies, underscoring therapeutic challenge [7]. In 10-20% of resistant tumours, ER expression is lacking, indicating that alternative pathways may assist tumourigenesis [14]. Notably, Androgen Receptors (AR), observed in 80-90% of ER-positive BCs, May substitute for ER by sustaining proliferation through ER- independent but nuclear receptor dependent mechanisms [6].

In resistant cases, ER function can be reactivated through altered transcriptional co-factors, growth factor-mediated kinase signaling, alterations in drug metabolism and efflux, or structural modifications within the ER complex [6]. ESR1 modifications observed in 20-40% of metastatic tumours, commonly impact the ligand-binding domain, reducing oestrogen dependency and evade treatment efficacy. This highlights the adaptive and evolving features of ER-positive BC under therapeutic pressure [15].

ERα and ERβ encoded by ESR1 and ESR2, and functions as transcription factors for ligand-activation regulating genomic expression through oestrogen response elements. Despite 96% identity in their DNA-Binding Domains (DBDs), ER isoforms exert divergent effects by recruiting varied co-regulators [15]. FOXA1 transcription factor enables ER-chromatin binding and governs ER-mediated transcriptional programs in ER-positive tumours [6]. Expression modifications to disrupt ER signaling foster unlimited growth and ET resistance [12].

PR-expression demonstrate improved outcomes in BC; however, PR may inconsistently initiate survival pathways *via Bcl-2* and cyclin D1 upregulation [9].Furthermore, membrane-bound PRs (mPRs) activate the mechanistic target of Rapamycin (mTOR), and phosphatidyl-inositol-3-kinase or Protein-kinase B (PI3K or Akt) pathways, improving resistance [16].

Long non-coding Ribonucleic acid (lncRNAs), including Down Syndrome Cell Adhesion Molecule–Antisense RNA 1 (DSCAM-AS1), reinforce ESR1 expression in tamoxifen-resistant models, further activating endocrine resistance and causing a potential therapeutic target [17].

Progesterone Receptor (PR) Modulation of Oestrogen Receptor (ER) in Invasive Ductal Carcinoma (IDC)

Modulating ER activity by progesterone in IDC plays an important role in hormonal interaction of IDC, substantially influencing BC pathogenesis. ER signaling prominently improves tumour proliferation and survival in HR-positive BCs, including IDC. The transcriptional activity of ER is regulated by co-regulators, chromatin-modifying proteins, and interacting pathways. Among these, PR has risen as a chief modulator of ER-dependent transcriptional processes. The ER-associated transcription is prominently affected by PR-specific tumours, subsequently impacting tumour phenotypes and response to treatment [18].

Evidence suggested that the anti-apoptotic proteins including *Bcl-2* are often expressed in ER+/PR+ IDC progression. For instance, Park SH et al., revealed tumour co-expression including ER and PR displayed *Bcl-2* elevation, highlighting the interplay contributing to survival signaling. This prototype suggested ER functioning enhancement by PR, thus, facilitating tumour development and ET resistance. Furthermore, deregulated PR signaling pathways may modify dependence on RR mechanisms, thereby elevating risk of endocrine resistance [19]. Various mechanisms of PR influence ER such as modifications in receptor-mediated processes and chromatin remodeling, and co-regulatory recruitment processes. The PR-B activation demonstrated by Kariagina A et al., through decreased expression of E-cadherins and Wnt pathway activation, facilitate establishment of invasive tumours [20].

The HR cross-talk including PR-A and PR-B isoforms influenced by PR-modulated ER activity exhibited modified ER signaling processes, thus leading to differentiation in ER-positive IDC management.

Key aspects	Chief Cellular/Molecular Features	Role in IDC Development	Hormone Receptor (HR)/ Signaling Pathways Involved	Key Findings
Tumourigenic variations and genomicin stability	Accumulated somatic mutations, chromosomal variations, and clonal evolution within ductal epithelial cells	Neoplastic transformation and progression towards IDC	PI3K/AKT and MAPK signaling processes	Genomic variations facilitate tumour initiation and progression within the ductal epithelial cells.
Ductal epithelial proliferation and structural expansion	Extended malignant epithelial cells with early preservation of ductal cells	Facilitates intraductal growth pattern before stromal invasion	Growth factor receptor (EGFR, HER family) signaling	Intraductal proliferation resulting from irregular activation of growth factor pathways.
HR signaling dysregulation	Overexpression or varied regulation of steroid HRs	Stimulates tumour cell proliferation, survival, and apoptosis resistance	Androgen Receptor (AR), Oestrogen Receptor (ER), PR depending on tumour context	HR signaling plays a crucial role in maintaining tumour growth and influencing therapeutic response
Growth factor receptor activation	Amplification or overexpression of receptor tyrosine kinases	Enhances downstream oncogenic signaling and cellular proliferation	HER2/ERBB2, EGFR, FGFR signaling cascades	Growth factor–mediated signaling promotes aggressive tumour phenotype and progression
Tumour microenvironment interactions	Crosstalk between tumour cells, immune cells, and stromal cells	Assists tumour survival, immune evasion, and local progression	Cytokine signaling, TGF-β pathway	Intraductal tumour resistance and progression stimulated by microenvironmental interactions
Epigenetic regulation	Histone modification and DNA methylation patterns	Genetic expression regulation involved in proliferation, differentiation, and apoptosis	HR–associated transcriptional regulation	Epigenetic modifications contributing to oncogenic activation and tumour progression.
Transition to invasive carcinomas	Breakdown of basement membrane and invasive phenotype acquisition	Marks progression from intraductal lesion to invasive carcinomas	EMT-related pathways, growth factor signaling	Molecular pathways accumulation leading to IDC

[Table/Fig-1]: Pathogenic mechanisms involved in IDC
(Abbreviations: DNA: Deoxyribonucleic Acid; EGFR: Epidermal growth factor receptor; EMT: Epithelial-to-Mesenchymal Transition; FGFR: Fibroblast growth factor receptor; HER2/ERBB2: Human epidermal growth factor receptor 2/Erb-B2 receptor tyrosine kinase 2; IDC: Invasive ductal carcinoma; MAPK: Mitogen-activated protein kinase; PI3K/AKT: Phosphoinositide 3-kinase/protein kinase B; TGF-β: Transforming growth factor beta).

The molecular mechanisms differentiating PR-A and PR-B are still under investigation; however, existing evidence supports their functionality in regulating ER targeted genetic expression and tumour progression, thus, establishing PR as a functional regulator and a significant therapeutic target [16].

HER2/neu Amplification and Aggressive Phenotypes

HER2/neu amplification represents a major molecular modification in IDC and is closely connected with aggressive biological overexpression and poor prognosis. The transmembrane tyrosine kinase receptors encoded by HER2/neu oncogenes play vital role in BC progression and IDC management. Amplification or overexpression of HER2/neu gene occurs in nearly 15-30% of BC cases and around 50% of DCIS cases, and is often linked to increased histological grade, decreased HR expression, increased proliferation, and unfavourable clinical outcomes [5], establishing HER2 as a vital biomarker for prognosis.

The HER2 activation facilitates tumourigenesis via receptor dimerisation and tyrosine phosphorylation, which commences downstream signaling pathways, including PI3K/Akt and MAPK pathways [19]. Such pathways enable aggressive tumourigenesis, cell-cycle advancement, differentiation, and apoptosis resistance. HER2 signaling also links with other regulatory mechanisms such as Transforming Growth Factor-beta (TGF-β), promoting autocrine secretion that enhances tumour mobilisation and invasion, thereby supporting IDC metastasis [21]. Furthermore, interplay between HER2, EGFR, and WNT/β-catenin signaling causes elevated mitogen activity, Epithelial-Mesenchymal Transition (EMT), and disrupted E-cadherin-driven cellular adhesion, thus improving tumour proliferation and interrupting adhesion [22]. Cross-talk between steroid receptors and HER2/EGFR signaling further improves endocrine responsiveness and therapeutic outcomes in BC [6].

HER2 heterogeneity is another well-defined characteristic of BC, indicating existence of distinct cancer cell population within same tumour, exhibiting varying frequency of gene amplification or protein expression. As per the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) 2009 guidelines, the HER2 genetic heterogeneity is frequent in BC, including IDC, though majority depict HER2-negative amplification status [23]. Literature suggests significant variability in HER2/neu amplification patterns within IDC. For example, Latta EK et al., depicted amplification modifications between DCIS and adjacent invasive tumour regions, suggesting that HER2/neu amplification exist in the in-situ components but not sustained in the invasive clone, indicating clonal evolution during IDC progression [24]. Similarly, Shin SJ et al., identified intratumoural HER2 amplification heterogeneity using tissue microarrays in around 16% of grade-3 IDCs [25]. Furthermore, Brunelli M et al., determined genotypic intratumoural heterogeneity in IDC with HER2 amplification, specifically in tumours featured by low-level amplification or chromosome 17 polysomy, influencing tumour behaviour and trastuzumab therapeutic response [23]. Additional evidence has correlated HER2 amplification with tumour aggressiveness; for instance, Bahremani HM et al., utilised Chromogenic In Situ Hybridisation (CISH) for demonstrating association between higher-grade IDC and HER2 amplification [26], while Shokouh TZ et al., reported association between HER2 overexpression and enhanced tumour grade, lymph node metastasis, and proliferative markers, like p53 and Ki-67 [27].

From therapeutic aspect, HER2 targeted therapies have potentially enhanced outcomes in HER2-positive BC. Trastuzumab, a human monoclonal antibody targets the HER2 extracellularly by hindering receptor dimerisation and thereby suppressing MAPK and PI3K/Akt signaling pathways, while also enhancing antibody-dependent cellular cytotoxicity, enabling suppressed tumour cell proliferation and survival [28]. In addition, combination of HER2-targeted regimens involving pertuzumab, antibody–drug conjugates like trastuzumab-deruxtecan or trastuzumab-emtansine, and small-molecules tyrosine kinase inhibitors namely tucatinib, lapatinib, or neratinib, have emerged to enhance tumoural sensitivity and overcome resistance [29]. Combination therapies targeting both cancer stem cells and differentiated malignant cells have emerged as efficient strategies to decrease recurrence frequencies and enhance long-term outcomes [28].

Regular HER2 examination facilitates strategies for directing treatment of BC including decisions related to chemotherapy and targeted ETs. HER2-positive is a response predictor to chemotherapeutic agents including anthracyclines and topoisomerase inhibitors, but may also associate with endocrine resistance due to the HER2-mediated activation of alternative signaling pathways [28]. However, current trials are enhancing trastuzumab-based regimens to address endocrine resistance and improve efficacy in IDC [28].

In contrast, HR+/HER2- BC is a frequent early-stage BC type, comprising around 70% of all diagnosed BCs [30]. Although ET remains standard treatment, recurrence is experienced still by few patients, leading to addition of CDK4/6 inhibitors (CDK4/6i) to Alexiou S et al., in a meta-analysis revealed efficacy of CDK4/6i represented by ribociclib, palbociclib, abemaciclib and dalpiciclib with ET with improved invasive disease-free survival and also demonstrated favourable trend in distant recurrence free-survival in early stage HR+/HER2-BC [30]. Moreover, Fedele P et al., demonstrated efficiency of CDK4/6 inhibitors plus ET in elderly patients (aged ≥80 years) with HR+/HER2- metastatic BC, further underscoring the evolving role of targeted therapeutics in tumour management [31].

Biomarkers and Personalised Treatment Approaches

ER and PR as Predictive Markers for Endocrine Therapy (ET): For understanding hormone-responsive BC, ER and PR have been identified using routine Immunohistochemistry (IHC) as validated predictive markers for ET. Tumours are classified as HR-positive if at least 10% of invasive cells exhibit ER and/or PR expression, thereby qualifying patients for ET unless evaluated as low-risk [2]. Recent evidence indicates that patient executing 1 to 10 percent HR expression may benefit form ET, thereby challenging the traditional 10 percent threshold [4].

The PR is constantly linked to positive outcomes and may significantly predict the benefits of ET compared to ER. The Arimidex, Tamoxifen Alone or in Combination (ATAC) trial evaluated patients with ER+/PR- tumours and improved outcomes with aromatase inhibitors rather than antioestrogens, suggesting therapeutic efficacy of PR expression [32].

The ER–/PR+ subtype, observed in 1-4% of cases, depict paucity of reproducibility. Gene Expression Microarray (GEM) dataset analysis and the Nurse's Health Study (NHS) indicated recategorisation of most of the ER–/PR+ tumours, with PR micro-RNA serving as a prognostic predictor solely in ER-positive cancers. Moreover, adding PR protein provides minimal prognostic value beyond ER status and clinical variables [27].

In DCIS, HR subtyping is prognostically significant; with tamoxifen markedly enhancing survival in ER-positive/PR-positive patients [13]. The Early Breast Cancer Trialists' Collaborative Group reported a reduction of 41% in relapse and a 34% decrease in mortality for ER-positive cases managed with tamoxifen for five years [33].

Resistance Mechanisms and Therapeutic Challenges

In IDC, mechanisms of resistance lead to considerable therapeutic limitations by allowing tumour cells to overcome treatment. Drug efficacy may be reduced by changes in drug metabolism, particularly through enzymatic degeneration. Additionally, drug integration, transportation, and retention are affected by changes in the

organisation of cell membrane. Of various known mechanisms of resistance, important one are ATP-dependent transporters including P-glycoprotein (P-gp),BC resistance proteins, and Multidrug Resistance Protein (MRP), which release chemotherapeutic agents effectively, leading to decreased intra-cellular concentration and promotion of multidrug resistance [29].

Treatment is complicated by genetic and epigenetic alteration by interference in apoptosis, functionality of HR, and regulation of cell cycles. In drug-resistant tumours, the *MDR1* gene and its by-product (P-gp) are overexpressed, leading to improved clearance of drug and decreased therapeutic efficacy [29]. This resistance can be addressed by nanoparticle-based drug delivery systems and efflux pump inhibitors. As IDC is heterogeneous, treatment optimisation can be done by targeting specific resistance pathways, including molecular profiling and EMT regulatory mechanisms [11].

Emergent Biomarkers and Combination therapeutics

The IDC management has seen significant modification through novel biomarkers and combination therapies, enabling efficient and tailored interventions. Furthermore, assessing HER2 status through Fluorescence In Situ Hybridisation (FISH) and IHC integration leads to concordant surgical samples and core tissues biopsies. Primarily, HER2 status recognition enables clinicians to personalise neoadjuvant mechanisms and delivers diagnostic data [26]. Furthermore, novel genomic targets such as ESR1 and HER2 modifications, along with other mutations, have been included in clinical practice for categorising IDC patients, probably benefiting from novel combination therapies [15].

PARP inhibitors (PARPi), including olaparib and talazoparib, are FDA-approved and emerged as an efficient targeted therapies for germline BRCA-mutants, metastatic HER2-negative or early-stage BC, including IDC. They serve as synthetic lethal agents by inducing cancer cell apoptosis, thereby delivering better efficacy with favourable safety profile compared to traditional chemotherapeutic agents [34]. Clinical trials have assisted PARPi efficacy and safety: the OlympiA clinical trial demonstrated that olaparib was linked to invasive-free and disease-free survival among patients experiencing HER2-negative early BC with germline BRCA1 or BRCA2 pathogenic variants following chemotherapy completion [34]. Similarly, the EMBRACA trial demonstrated that talazoparib significantly enhanced progression-free survival and patient-reported outcomes compared to standard chemotherapy among patients with germline BRCA-mutated HER2-negative metastatic BC [35].

Clinical Implications and Future Perspectives

Current guidelines for biomarker-based treatment: With the advent of molecular diagnostics, proteomics, and genomics, evolution of biomarker-based treatment guidelines in IDC management have occurred, facilitating enhanced patient stratification and personalised therapy. This framework involves histopathology combined with the evaluation of molecular biomarkers. Key biomarkers including ER, PR, HER2/neu, and Ki-67 are routinely assessed to generate prognosis and guide treatment [4].

The National Comprehensive Cancer Network guidelines suggest standardised biomarker testing in all BC patients, primarily using IHC and FISH, particularly for HER2 assessment. In HR+/HER2– BC, *PIK3CA* mutations assessment through tumour tissue or liquid biopsy is recommended to determine eligibility for Alpelisib combined with fulvestrant treatment. For negative liquid biopsy outcomes, tumour testing is recommended subsequently [27]. The procedures developed by the College of American Pathologists and American Society of Clinical Oncology recommend the significance of precision and consistency examination across laboratories [24]. Neagu AN et al., identified deregulated proteins that could function as novel biomarkers, thereby increasing IDC stratification and targeted treatment in upcoming guidelines [7].

Personalised Therapy and Patient Outcomes

Integrating multigene assays into clinical decision-making has significantly progressed personalised therapy and improved outcomes in IDC. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, tamoxifen-treated cases exhibit lower recurrence scores (<18) demonstrating a 10-year long recurrence risk of nearly 7%, in contrast to intermediate (18-30) and high (≥31) scores facing recurrence risks of 14% and 31%, respectively [36]. The Oncotype DX 21-gene assay comprehensively validate relapse risk, and predict advantages of chemotherapeutic regimens [37]. These outcomes validated the assay's prognostic ability and contributed to modifications in clinical practice during the 2004.

The NSABP B-20 trial further validated the predictive utility of assay. ER-positive, and node-negative status, showed significant improvement of 10-year long disease-free survival in high-risk cohort, increasing from 60% to 88%, while no advantage observed in the low-risk groups with the addition of chemotherapy to tamoxifen [36]. Similarly, the Southwest Oncology Group-S8814 trial reported improved consequences with chemotherapy in HR-positive, and node-positive patients revealing high scores; however, findings with intermediate-risk patients were limited by sample size and follow-up duration [38].

The trial assigning individualised options for treatment improved risk stratification by focusing on recurrence scores ranging between 11 to 25. Women aged over 50 years, depicted non-inferiority with ET alone than combination therapy, with 9-year invasive disease-free survival rates of 83.3% compared to 84.3%. While women under 50 demonstrated a positive response to chemotherapy, even in the intermediate range [38]. Furthermore, MINDACT and RxPONDER (A Clinical Trial Rx for Positive Node, Endocrine Responsive BC), has augmented these methodologies by including genomic and clinical variables for determining candidates for chemotherapy accurately [39,40]. These results validate the significance of multigene assays in improving patient outcomes and tailoring treatment of IDC.

Advances in Molecular Targeting Strategies

For IDC, the development of molecular targeting strategies has been fueled by advancements in multi-omics technologies. Large-scale data generation and analysis in a variety of fields, such as proteomics, epigenomics, genomics, transcriptomics, metabolomics, and interactomics, have been made possible by mass spectrometry imaging, single-cell, and next-generation sequencing techniques [41]. These platforms have enhanced the understanding of IDC pathobiology and its development from DCIS. Based on the whole-exome sequencing, IDC exhibits clonal selection and greater intra-lesion heterogeneity, while DCIS and IDC have similar copy number profiles [41].

Single-cell genetic analyses have revealed persistent differences linked to invasiveness, such as MYC amplification. Biomarkers, such as FGF2, GAS1, and SFRP1, have been shown by genetic expression profiling to differentiate invasive cells from stationary cells and suggest early metastasis [42]. Interestingly, according to epigenetics data, primary DNA methylation changes may be important predictors of tumour progression. While single-cell RNA sequencing revealed indications unique to the tumour microenvironment, transcriptomic methods such as reverse transcription quantitative polymerase chain reaction and RNA sequencing confirmed aggressive DCIS markers, including MMP11 and COL10A1 [7]. Overexpression of HER2 and JAM-A are observed in aggressive DCIS, using proteomic methods that include isobaric tags for absolute and relative quantification and ion spectra–mass spectrometry [43]. Real-time representation

of IDC is made possible by modern diagnostic methods, such as intraoperative regulation tools like MassSpec Pen and hydrogel-based nanoparticles [7].

Future Directions Relevant to IDC Research

Management of IDC has advanced mainly due to recent developments in customised diagnostic techniques, molecular profiling, and therapeutic approaches. It is critical to comprehend clinical determination and validation of novel biomarkers to accurately depict treatment response. Interestingly, stromal biomarkers, such as fibrosis factors and CD204-positive tumour-specific macrophages, are linked to higher recurrence rates, highlighting their potential to improve risk assessment and guide adjuvants [44]. Additionally, immune-modulating processes, including PD-1, PDL-1 overexpression, CTLA-4, and indoleamine-2,3 dioxygenase are therapeutically targeted and significantly improve anti-tumour immunity as treatment targets [43]. The targeted PD-L1 axis has been linked to cytokine T-lymphocytes, which may improve favourable outcomes for immune-suppressive patients. Similarly, phase I clinical trial included patients with HER2-negative BC and represented therapeutic benefits of ipilimumab in combination with nivolumab which is an anti-PD-1 monoclonal antibody [45].

Artificial Intelligence (AI) uses integrated workflows and thus enhances diagnostic accuracy. Additionally, thorough AI algorithms effectively identify BC in biopsy samples and interpret genomic, proteomic, transcriptomic, and radiological data in real-time, thereby supporting the implementation of customised treatments [46]. Sphingolipid metabolism-related molecular evidence highlighted drug development with novel therapeutic targets and predicted particular genes associated with aggressive IDC phenotypes [14]. Finally, biomarkers-assisted de-escalation approaches are gaining momentum for decreasing unnecessary management while preserving quality of life, recommending a marked shift in treatment of IDC.

Limitation(s)

This comprehensive review has several limitations. First, the study lacked systematic literature search and normalised inclusion criteria may have generated selection bias. The synthesis was dependent on the authors' evaluation of the literature, which could contemplate subjective assessments. Additionally, relevant literature, particularly non-English or unpublished resources, may have been skipped. The included studies differing in quality, but no formal quality appraisal was performed. As a comprehensive review, no quantitative synthesis was done, constraining the ability to assess the strength of associations. Finally, with continuing developments in IDC research and therapeutic strategies implementation, some recent evidence might not have been apprehended.

CONCLUSION(S)

The complex interaction between growth factors and HRs influences IDC pathogenesis with ER signaling processes facilitates tumour progression, while PR-modulated ER signaling processes facilitates treatment responses. Activation of HER2/neu improves aggressiveness through the PI3K/Akt and MAPK processes Along with conferring resistance in association with ER/PR pathways. Multi-omics development exposed biomarkers to improve therapeutic response and enable tailored management strategies. Emerging techniques, such as HER2 inhibition, antibody-drug conjugates, and AI-driven therapeutics, improve outcomes for patients with IDC by facilitating early tumour identification and selection of therapy.

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