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Review of 10 years of research on breast cancer patients: Focus on indoleamine 2,3-dioxygenase

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Abstract

Therapeutic manipulation of the immune system in cancer has been an extensive area of research in the field of oncoimmunology. Immunosuppression regulates antitumour immune responses. An immunosuppressive enzyme, indoleamine 2,3-dioxygenase (IDO) mediates tumour immune escape in various malignancies including breast cancer. IDO upregulation in breast cancer cells may lead to the recruitment of regulatory T (T-regs) cells into the tumour microenvironment, thus inhibiting local immune responses and promoting metastasis. Immunosuppression induced by myeloid derived suppressor cells activated in an IDO-dependent manner may enhance the possibility of immune evasion in breast cancer. IDO overexpression has independent prognostic significance in a subtype of breast cancer of emerging interest, basal-like breast carcinoma. IDO inhibitors as adjuvant therapeutic agents may have clinical implications in breast cancer. This review proposes future prospects of IDO not only as a therapeutic target but also as a valuable prognostic marker for breast cancer.

Key Words: Indoleamine 2,3-dioxygenase; Breast cancer; Therapeutic target; Prognostic marker; Immune responses; Immune escape

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INTRODUCTION

Breast cancer is the most common cancer in women worldwide. A variety of genetic and non-genetic factors can be linked to breast cancer. Recent emerging epidemiologic, preclinical, and clinical data suggest the key role of the immune system in the aetiology of breast cancer[1]. The current understanding of the molecular and cellular mechanisms underlying cancer development suggests that immune cells functionally regulate epithelial cancer development and progression[2]. The innate and adaptive immune systems play a role in preventing relapse in breast cancer[1]. Lymphocytes, including T cells, T-regs, natural killer (NK) cells, and their cytokine release patterns are associated with both primary prevention and relapse of breast cancer[1,3]. Hence, breast cancer prognosis may be related to the functional status of the immune system.

Breast cancer cells can evade immune responses, by various immunosuppressive mechanisms, such as the upregulation of indoleamine 2,3-dioxygenase (IDO/IDO-1)[4, 5]. IDO is a heme-containing immunosuppressive enzyme, that degrades the essential amino acid L-tryptophan into kynurenine[6]. IDO is involved in the immune homeostasis and immune-related functions not only during pregnancy but also in chronic inflammatory diseases and tumour immune-escaping mechanisms[7-9]. IDO is chronically triggered in cancer patients[10]. Deprivation of tryptophan directly affects the cytotoxicity of T cells. In addition, the toxic metabolites produced from tryptophan degradation directly induce T cell apoptosis *in vitro*[9]. IDO may inhibit T cell immunity by inducing the differentiation and maturation of T-regs[11]. IDO overexpression induces immunosuppression and tolerance[8]. IDO-expressing cells are found at several sites of immune tolerance, including thymus, placenta, anterior chamber of the eye, mucosa of the gut and epididymis[12-14]. Human monocyte-derived macrophages and dendritic cells (DCs) express IDO[15,16]. IDO-expressing DCs are found in breast tumour tissue as well as draining lymph nodes of patients with breast cancers[17]. IDO expression may suppress immune responses by blocking NK cells (Figure 1)[18]. However, the immunosuppressive role of IDO in tumour immunology and its associations with other tolerogenic mechanisms have only recently begun to be elucidated. The molecular mechanisms underlying tumour immune escape are currently the topic of active research. In this review, we examine the potential role of IDO as a prognostic marker and therapeutic target in breast cancer patients.

IMPACT OF IDO ON BREAST CANCER PATIENTS

It has been established that IDO in the tumour microenvironment has the capacity to inhibit antitumour immunity and promote metastasis, both hallmarks of cancer[19]. It is evident that IDO is consistently and robustly expressed in breast cancer[20]. IDO is suggested to play a pivotal role in the pathogenesis of breast cancer (Table 1). In 2011, Yu *et al*[21] observed that the upregulation of IDO in primary breast cancer might inhibit the local immune response by the infiltration of T-regs into the tumour microenvironment thereby promoting metastasis[21]. In 2013, Yu *et al*[22] further investigated IDO expression in myeloid-derived suppressive cells in breast cancer and observed that STAT3-dependent IDO expression induced the immunosuppressive effects of myeloid derived suppressor cells in breast cancer[22]. IDO has recently received more attention because of its involvement in regulating angiogenesis[23]. Wei *et al*[23] studied the effects of IDO on microvessel density and reported that high IDO expression is associated with microvessel density; causes a poor prognosis and subsequently promotes angiogenesis in breast cancer[23].

Table 1 Review of ten years of research on indoleamine 2,3-dioxygenase in breast cancer patients

Year	Ref.	Population	Description
2011	Yu <i>et al</i> [21]	Chinese (<i>n</i> = 26)	IDO upregulation inhibits local immune responses by infiltration of T-regs in the tumour microenvironment and promotes metastasis in breast cancer
2011	Lyon <i>et al</i> [27]	American (<i>n</i> = 33)	Increased tryptophan degradation may occur in women with early-stage breast cancer
2012	Jacquemier <i>et al</i> [31]	French (<i>n</i> = 1749)	Immunodetection of IDO-positive cells may be used for diagnosis of medullary breast cancer. IDO has a prognostic significance in basal like breast cancer
2013	Soliman <i>et al</i> [24]	American (<i>n</i> = 203)	IDO expression was higher in ER ⁺ breast cancer than ER ⁻ breast cancer
2013	Yu <i>et al</i> [22]	Chinese (<i>n</i> = 85)	STAT3-dependent IDO expression induces immunosuppressive effects of MDSCs in breast cancer
2014	Bi <i>et al</i> [37]	Chinese (<i>n</i> = 110)	IDO and EGFR may serve as a potential biomarkers for breast cancer prognosis and treatment
2014	Isla Larrain <i>et al</i> [32]	Argentinian(<i>n</i> = 91)	IDO was expressed in a TNBC subgroup and was involved in the tumour immune escape
2015	Salvadori <i>et al</i> [33]	Brazilian (<i>n</i> = 20)	IDO inhibitor when combined with paclitaxel may be used as a new therapeutic strategy for breast cancer
2017	Kim <i>et al</i> [30]	South Korean (<i>n</i> = 200)	IDO might be an effective immunotherapeutic target in TNBC
2017	Dewi <i>et al</i> [25]	German (<i>n</i> = 15)	IDO-1 expression in ER ⁻ breast cancer may be associated with poor prognosis. IDO-1 maybe a promising therapeutic target for ER ⁻ breast cancer
2017	Carvajal-Hausdorf <i>et al</i> [36]	American (<i>n</i> = 362)	IDO-1 quantification has potential to differentiate a population that might get an advantage from IDO-1 blockade
2017	Li <i>et al</i> [38]	Chinese (<i>n</i> = 46)	Expression of IDO and IL-6 is associated with advanced breast cancer and poor response to neoadjuvant chemotherapy
2018	Ye <i>et al</i> [34]	Chinese (<i>n</i> = 963)	IDO and programmed cell death protein-1 pathways might be an effective therapeutic approach in breast cancer treatment
2018	Wei <i>et al</i> [23]	Chinese (<i>n</i> = 65)	IDO may induce angiogenesis in breast cancer, providing a molecular or gene therapy target for angiogenesis inhibition
2018	Li <i>et al</i> [39]	Chinese (<i>n</i> = 44)	Tumour-infiltrating T-regs, MDSCs and IDO expression may be used as a prognostic marker for the outcome of neoadjuvant chemotherapy
2018	Dill <i>et al</i> [29]	American (<i>n</i> = 281)	IDO expression in high-grade,TNBC is associated with PD-L1 co-expression
2019	Asghar <i>et al</i> [28]	Pakistani (<i>n</i> = 100)	IDO expression in TNBC may suggest its role in disease pathogenesis
2019	Onseti <i>et al</i> [26]	Belgian (<i>n</i> = 202)	Kynurenine/tryptophan ratio in plasma might differentiate breast cancer patients from healthy controls
2019	Asghar <i>et al</i> [35]	Pakistani (<i>n</i> = 100)	IDO expression is associated with COX-2 expression in breast cancer patients
2019	Zhao <i>et al</i> [40]	Chinese (<i>n</i> = 53)	IDO expression and activity is linked with advanced breast cancer and poor response to neoadjuvant chemotherapy
2020	Wei <i>et al</i> [41]	Chinese (<i>n</i> = 77)	IDO and tumour infiltrating immune cells can help to evaluate the prognosis of breast cancer patient

IDO: Indoleamine 2,3-dioxygenase; T-regs: regulatory T cells; ER: Estrogen receptor; TNBC: triple-negative breast cancer; STAT3: Signal transducer and activator of transcription 3; MDSCs: Myeloid-derived suppressor cells; EGFR: Epidermal growth factor receptor; COX-2: Cyclooxygenase-2.

Soliman *et al*[24] also examined IDO expression in breast cancer patients (*n* = 203). IDO overexpression was detected in ER⁺ tumours but not ER⁻ tumours. Overall survival was better in ER⁺ patients with high IDO expression. This study provided a new prospective for ongoing clinical trials of IDO inhibitors in metastatic breast cancer. They proposed further studies to understand the complex role of IDO in the natural progression of breast cancer at different stages of the disease[24]. Another study published by Dewi *et al*[25] demonstrated that increased IDO expression in ER⁻ breast cancer might influence its malignant phenotype and result in a poor prognosis [25].

The kynurenine to tryptophan (Kyn/Trp) ratio is used to measure IDO enzymatic activity. Onesti *et al*[26] measured IDO activity in breast cancer patients (*n* = 202) with all subtypes and healthy controls (*n* = 146). They reported that the Kyn/Trp ratio might differentiate breast cancer patients from healthy controls[26]. A similar study conducted by Lyon *et al*[27] compared the levels of tryptophan degradation in women

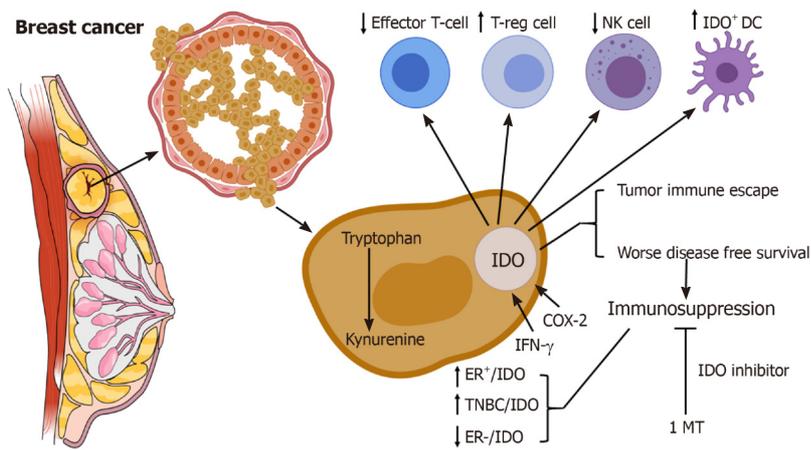


Figure 1 Indoleamine 2,3-dioxygenase inhibition as potential immunotherapeutic strategy for breast cancer. Indoleamine 2,3-dioxygenase (IDO) is heme-containing immunosuppressive enzyme. IFN- γ is a potent inducer of IDO. Cyclooxygenase-2 expression by tumour cells stimulates intrinsic tumour expression of IDO. IDO degrades tryptophan into kynurenines. Deprivation of tryptophan directly affects the cytotoxicity of T cells. IDO may inhibit T cell immunity by inducing the differentiation and maturation of T-regs. IDO expression could suppress immune responses by blocking natural killer cells. IDO⁺ dendritic cells are found in breast tumour as well as axillary lymph nodes of these patients. High IDO expression is observed in ER⁺ tumours than ER⁻ tumours. IDO is expressed in a triple-negative subgroup. IDO expression is associated with tumour immune escape and overall survival of the patients. 1-MT is the pharmacological inhibitor of IDO. IDO: Indoleamine 2,3-dioxygenase; COX-2: Cyclooxygenase-2; NK: Natural killer; ER: Estrogen receptor.

with or without breast cancer and observed an increased Kyn/Trp ratio in women with breast cancer. Keeping in view the multifactorial role of IDO, the authors suggested that further research was necessary to determine the relationships among these important biological factors and neuropsychiatric symptoms in women with breast cancer[27].

IDO IN TRIPLE-NEGATIVE BREAST CANCER

Due to advancements in early diagnosis and treatment of breast cancer, the overall survival of patients has significantly improved over the years. Nevertheless, triple-negative breast cancer (TNBC) is a more aggressive tumour than other breast cancers [28]. Our recent data showed high IDO expression in TNBC patients. Furthermore, we observed that high IDO expression was significantly correlated with decreased overall survival[28]. Dill *et al*[29] also observed IDO expression among high-grade TNBC. In addition, they determined that IDO expression was associated with PD-L1 co-expression. They suggested clinical trials to assess the effectiveness of IDO inhibition relative to IDO expression as well as its role when combined with anti-programmed cell death protein 1 (PD-1)/PD-L1 immunotherapy[29]. Another study by Kim *et al*[30] was conducted to evaluate the clinical and pathological characteristics of an IDO-expressing TNBC subset, and the authors observed that IDO positivity was associated with the basal-like phenotype. They also suggested the role of IDO blockade in the treatment of TNBC patients[30].

Among the molecular subtypes of breast cancer, basal-like breast carcinoma (BLBC) has the poorest outcomes[31]. Jacquemier *et al*[31] determined that IDO was overexpressed at the transcriptional and translational levels in a subset of TNBC. They elaborated that IDO overexpression was correlated with morphological medullary features and had autonomous prognostic significance in BLBC. Medullary breast carcinoma (MBC) had a better prognosis than non-MBC, but IDO was overexpressed at the mRNA level in BLBC and MBC compared with non-MBC. IDO expression is thus correlated with tumour infiltrating lymphocytes, which are present in both MBC and BLBC. IDO overexpression in BLBC with a favourable prognosis may be due to kynurenines, which have the capacity to induce apoptosis in lymphocytes as well as tumour cells[31]. Another study revealed that IDO was mostly expressed in the TNBC subtype. The same authors also observed IDO expression in breast cancer and circulating microvesicles from breast cancer patients with advanced stages[32].

THERAPEUTIC AND PROGNOSTIC SIGNIFICANCE OF IDO

IDO inhibitors have therapeutic significance when given in combination with chemotherapeutic agents for breast cancer treatment[33]. An IDO inhibitor (1-methyl-DL-tryptophan) in combination with paclitaxel may be a new therapeutic strategy for breast cancer[33]. Several studies support this hypothesis; for instance, Ye *et al*[34] investigated the association between IDO and PD-1 in the tumour microenvironment and in tumour-draining lymph nodes in breast cancer patients. They observed a positive association between the expression of IDO and PD-1. The team also proposed that inhibiting both of these pathways might act as a novel therapeutic strategy in breast cancer treatment[34]. Another study published by Asghar *et al*[35] reported that high IDO expression was correlated with high cyclooxygenase-2 expression in breast cancer patients. It was suggested that the simultaneous targeting of cyclooxygenase-2 and IDO may have potential for treatment of breast cancer[35]. Carvajal-Hausdorf *et al* [36] observed that the IDO protein was expressed in hormone receptor-positive breast cancer. Furthermore, IDO was negatively correlated with B-cell infiltration in tumours, and high IDO expression was associated with poor overall survival. The authors proposed that IDO quantification has the potential to differentiate a population that might obtain an advantage from IDO-1 blockade[36].

IDO has not only therapeutic significance but also prognostic significance. Bi *et al* [37] observed the co-expression of IDO and epidermal growth factor receptor (EGFR) in breast cancer and suggested that IDO and EGFR may serve as potential biomarkers for breast cancer prognosis and treatment[37]. Another study conducted by Li *et al*[38] in 2017, aimed to investigate the co-expression of IDO and interleukin-6 in breast cancer patients prior to neoadjuvant chemotherapy. They observed that IDO and interleukin-6 expression was related to advanced breast cancer and a poor response to neoadjuvant therapy[38]. In 2018, Li *et al*[39] further explored whether tumour-infiltrating T-regs, myeloid-derived suppressor cells and IDO expression may be used as prognostic markers for the outcome of neoadjuvant chemotherapy[39]. Additionally, Zhao *et al*[40] observed that high IDO expression and activity were associated with advanced disease, a poor prognosis and chemoresistance in breast cancer[40]. In 2020, Wei *et al*[41] identified tumour infiltrating immune cells, and IDO and PDL-1 expression in breast cancer patients. The authors proposed that IDO in combination with tumour infiltrating immune cells might help to assess the prognosis of patients with breast cancer[41].

FUTURE PROSPECTS

IDO is involved in the regulation of the immune system. Upregulated IDO is associated with a poor prognosis in various cancers[42-44], but in the case of BLBC, high IDO expression indicates a favourable prognosis[31]. Another study revealed improved overall survival among ER⁺ breast cancer patients with high IDO expression [24]. However, several studies carried out regarding IDO involvement in breast cancer showed that IDO overexpression was associated with breast tumour growth and metastasis[4,21,45,46]. In view of the contradictory findings, further studies are therefore required to understand the complex role of IDO in breast cancer. Identification of more efficient and less toxic IDO inhibitors is urgent. Currently, two IDO inhibitors are in a clinical development stage as immunotherapeutic agents in breast cancer treatment. These inhibitors are Indoximod (NLG2101) developed by NewLink Genetics[47] and INCB024360 developed by Incyte[48,49]. Two therapies have been exclusively designed to treat HER2-positive breast cancer in combination with the AD.p53 DC vaccine and docetaxel (NCT01042535 and NCT01792050 respectively)[50]. IDO inhibitors as adjuvant therapeutic agents may have clinical implications in breast cancer[33]. Targeted IDO inhibition using nanoparticles may provide a better outcome. Tryptophan-2,3-dioxygenase (TDO) has biochemical activity similar to that of IDO[51, 52]. Apart from IDO, another isoform IDO-2 has also been discovered[53,54]. Both IDO-2 and TDO are involved in the degradation of tryptophan[55]. Future studies should focus on the role of IDO-2 and TDO in breast cancer.

CONCLUSION

The therapeutic implications of IDO are unquestionable but its potential as a prognostic biomarker may have significant outcomes.

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