INDOLEAMINE 2,3 DIOXYGENASE AS AN IMMUNOTHERAPEUTIC TARGET BRINGS A NEW HOPE FOR CANCER PATIENTS

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Abstract

Therapeutic manipulation of immune system in cancer has been an extensive area of research in the field of oncoimmunology. Immunotherapy helps the immune system to combat against cancer. Tumour cells take an edge of immunosuppressive mechanisms and inhibit antitumour immune responses. Indoleamine 2,3-dioxygenase (IDO) is an immunosuppressive enzyme which is involved in tumour immune escape mechanism in various cancers. IDO can degrade the tryptophan into kynurenines and has an ability to enhance the immune tolerance through mammalian target of rapamycin pathway general control nonderepressible 2 (GCN2) pathway and induction of regulatory T (T-regs) cells. IDO-induced T-regs suppress the local immune responses in the tumour microenvironment and promote metastasis. IDO overexpression in various cancers is associated with poor prognosis. Several preclinical and clinical trials have been proceeding and recommend that IDO inhibitor may be an influential tool against a wide range of cancers. IDO inhibitors as adjuvant therapeutic agents may also have clinical implications. Thus, IDO has the potential to be used as an immunotherapeutic target. This review discusses the promising role of IDO in cancer and its implication in immunotherapy.

Key words: Breast cancer, colorectal cancer, haematological malignancies, immunotherapy, indoleamine 2,3-dioxygenase, pancreatic cancer, prostate cancer

Introduction

Immunotherapy uses specific parts of an individual's immune system to fight against cancer. Cancer immunotherapy is promptly progressing and now is considered as the "fifth pillar" of cancer therapy.[1] Immunotherapeutic approaches include adoptive cellular immunotherapy, cancer vaccines, oncolytic viruses and immune checkpoint blockade.[2] It has been established that the defective immune system plays a critical role in cancer development.[3] Some malignant cells have the capacity to manipulate their own characteristics as well as cells in their microenvironment to form "successful" tumours thus evading the tumour immunosurveillance system.[1] Cancer cells can escape the immune attack through various complex mechanisms, including tumour induced immunosuppression through the upregulation of immunosuppressive enzymes, such as indoleamine 2,3-dioxygenase (IDO/IDO1).[4,5] IDO is a heme-containing enzyme involved in tryptophan catabolism.[6] IDO induces immunosuppression through tryptophan degradation and generation of tryptophan metabolites.[6] Tryptophan degradation by IDO directly affects T-cell proliferation through the activation of the GCN2 kinase pathway.[7] Tryptophan metabolites (Kynurenines) also have the potential to induce apoptosis in lymphocytes.[8] T-cell immunity may be inhibited by IDO through induction of differentiation and maturation of T-regs.[9] Overexpression of IDO is involved in immunosuppression and tolerance.[10] IDO producing cells are found at various immune tolerance sites, including thymus, placenta, anterior chamber of eye, mucosa of gut and epididymis.[11-13]

IDO is expressed by human monocyte-derived macrophages and dendritic cells (DC).[14,15] Role of IDO

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and its mode of action on cancer growth and immune evasion are still nascent in human cancer research. Numerous studies have documented a probable association between various clinical or immunologic parameters and IDO expression. Enhanced IDO expression in human cancer patients is linked with metastasis and predicts poor patient survival.[16] IDO is involved in tumour immune escape.[17] This review describes the involvement of IDO in various malignancies and proposes future prospects of IDO as immunotherapeutic target.

IDO in Breast Cancer

IDO protein is expressed in solid tumours such as breast cancer.[18] The involvement of IDO in breast cancer pathogenesis has been outlined in Table 1. IDO overexpression has an autonomous prognostic significance in basal-like breast carcinoma (BLBC) and is linked with morphological medullary features. Medullary breast carcinoma (MBC) has a better prognosis than non-MBC, but IDO is overexpressed at mRNA level in BLBC and MBC as compared to non-MBC. Tumour-infiltrating lymphocytes (TILs) reported in both MBC and BLBC. IDO expression is correlated with TILs.[19] IDO is involved in metastasis formation and tumour immune escape in

murine breast cancer cell lines as well. IDO^+ tumour grows faster than IDO^- tumours in immunodeficient severe combined immunodeficiency mice. IDO1 is involved in breast tumour growth and spontaneous pulmonary metastasis formation.[20] Soliman et al. analysed an expression of IDO protein in 203 breast cancer cases. IDO overexpression was observed in ER^+ (oestrogen receptor) tumour as compared to the ER^- tumours ($P = 0.0064$). This study gave a new dimension to the ongoing clinical trials of IDO inhibitors in the metastatic breast cancer. They proposed further studies to understand the complicated role of IDO in breast cancer progression at different stages of the disease.[21]

Another murine breast cancer model research provided evidence that gene silencing of IDO is a potent approach to enhance the efficacy of DC-based cancer immunotherapy. IDO-silenced DCs improve cytotoxic T lymphocyte activity and tumour antigen-specific T-cell proliferation. IDO targeted inhibition in DCs may be a convenient resolution to boost the efficiency of DC vaccine in clinics.[22]

IDO overexpression was found in myeloid-derived suppressive cells (MDSCs), extracted from fresh breast

Table 1: Comprehensive review of indoleamine 2,3-dioxygenase involvement in breast cancer

Year	Investigator	Description
2012	Jacquemier et al.[19]	IDO overexpression is associated with morphological medullary features and has independent prognostic value in BLBC
2012	Levina et al.[20]	IDO1 expression has immunological and non-immunological effects on breast tumour growth and spontaneous pulmonary metastasis formation
2013	Soliman et al.[21]	Higher IDO expression is observed in tumours with ER+phenotype than ER - tumours
2013	Zheng et al.[22]	IDO gene silencing may enhance the efficacy of (DC)-based cancer immunotherapeutic
2013	Yu et al.[23]	MDSCs suppress the anti-tumour immune responses by IDO expression in breast cancer
2014	Isla Larrain et al.[24]	*In vitro* and *in silico* gene expression revealed that IDO is expressed in a (TNBC) subgroup. IDO is involved in the tumour immune escape
2015	Salvadori et al.[25]	A decreased IDO expression is noted in cultured cancer cells of breast cancer patients when paclitaxel is given in combination with IDO inhibitor. It may be a new therapeutic strategy for breast cancer
2016	Chen et al.[26]	IDO inhibitors in combination with chemotherapeutic agents improve antitumor responses in breast cancer mouse model
2017	Kim et al.[27]	IDO expression is associated with BLBC. IDO inhibition may play a key role in the treatment of (BL) TNBC
2017	Noonepalle et al.[28]	IDO1 methylation regulates anti-immune responses in breast cancer subtypes. IDO methylation can be used as a prognostic biomarker for IDO inhibitor based immunotherapy

IDO: Indoleamine 2,3-dioxygenase, BL: BASAL-like, BLBC: BL breast carcinoma, DC: Dendritic cell, MDSCs: Myeloid-derived suppressive cells, TNBC: Triple negative breast cancer

cancer tissues. It was associated with a high frequency of forkhead box P3 (Foxp3[+)] T-regs in lymph node metastasis and tumours. The role of signal transducer and activator of transcription 3 (STAT3) in IDO expression and IDO-dependent MDSC-mediated immunosuppression on T cells was reported in this study.[23] IDO expression was detected in the sub-group of triple negative breast cancer (TNBC).

Furthermore, *in silico* studies verified the expression of IDO as well.[24] 1-Methyl-DL-tryptophan (D-1MT) is an IDO inhibitor which has therapeutic significance when given in combination with chemotherapeutic agents for breast cancer treatment.[25] Paclitaxel in combination with D-1MT decreased IDO expression in cultured cells from the breast tumour microenvironment.[25] Similar results were obtained in a breast cancer mouse model using NLG-919 (IDO inhibitor).[26]

A recently published data revealed that IDO1 expression is linked with TNBC with the BL phenotype and increased stromal lymphocytic infiltration. IDO1 immune checkpoint blockade may play a crucial role in the treatment of patients with TNBC.[27] Anti-immune responses exhibited by breast cancer subtypes are regulated by methylation of IDO1. IDO methylation can be used as a prognostic biomarker for IDO inhibitor based immunotherapy.[28]

IDO in Colorectal Cancer (CRC)

CRC is one of the major public health problems in the world.[29] The role of IDO in CRC has been outlined in Table 2. IDO1 expression is an independent prognostic factor in the pT1-4N1Mx-staged CRC.[30] Expression was associated with metachronous metastases and overall survival. IDO1 is a promising prognostic indicator in CRC identified by Ferdinande *et al*.[30] A murine model study indicates that IDO1 induces tumour proliferation and growth of neoplastic epithelium in a cell-autonomous fashion through activation of β-catenin signalling and kynurenine metabolites production. These results have considerable implications for IDO1 inhibitors as immunotherapeutic agents for IDO1- expressing colitis-associated and sporadic colonic neoplasms.[31]

Daniel *et al*. (2015) measured the activity of IDO in patients with CRC. Quantification of IDO enzymatic activity was performed through high-performance liquid chromatography (HPLC) in the serum of 68 patients. IDO activity was observed high in patients with CRC. They suggested an association between IDO activity and CRC; further studies on IDO activity are required to establish it as a reliable serum biomarker of CRC.[32]

A recently published data about IDO1 expression also revealed that it is involved in the progression of CRC and is linked with impaired clinical prognosis. In this study, they analysed the expression of IDO1 and beta-catenin proteins by immunohistochemistry on the tissue samples of 192 CRC patients. IDO1-regulated molecular pathway was demonstrated to upregulate abnormal beta-catenin expression in the nucleus and cytoplasm of CRC patients having a low mutation rate of adenomatous polyposis coli,

Table 2: Indoleamine 2,3-dioxygenase involvement in colorectal cancer

Year	Investigator	Description
2012	Ferdinande *et al*.[30]	High IDO1 expression at the tumour invasion is associated with (CRC) progression and correlates with impaired clinical outcome, implying that IDO1 is an independent prognostic marker for CRC
2013	Thaker *et al*.[31]	IDO1 is involved in colitis-associated tumorigenesis in mice. The epithelial cell-autonomous survival advantage supported by IDO1 to colon epithelial cells demonstrate its potential as a therapeutic target
2015	Eyraud *et al*.[32]	IDO activity is higher in patients with CRC compared with those without CRC. This study is the first step to establish that IDO enzymatic activity quantification is a reliable serum marker for CRC
2016	Chen *et al*.[33]	IDO1 regulated molecular pathway led to the abnormal expression of beta-catenin in the nucleus and cytoplasm of CRC patients with a low mutation rate of (APC), endorsing IDO1 is an appealing target for immunotherapy in CRC

CRC: Colorectal cancer, APC: Adenomatous polyposis coli, IDO: Indoleamine 2,3-dioxygenase

thus suggesting IDO1 an attractive immunotherapeutic target in CRC.[33]

Engin *et al*. indicated that high IDO immunostaining score is a strong predictor for lymph node metastasis.[29] IDO expression allows cancer subsets to evade immune attack in colorectal tumour cells. However, a suitable tool for the perseverance of undetected tumour cells does not exist that may be responsible for recurrent CRC. They recommended IDO immunostaining for histopathological evaluation of CRC cases.[29]

IDO in Haematological Malignancies

Haematological malignancies are cancers that affect the blood and lymph system. IDO expression and activity are upregulated in numerous haematological malignancies [Table 3]. Hoshi *et al*. investigated the expression of IDO in Adult T-cell leukaemia/lymphoma (ATLL) cell and the chemotherapeutic effect on IDO-initiating L-Tryptophan catabolism in ATLL patients. Level of IDO mRNA expression and enzymatic activity of IDO in ATLL cells were noticeably enhanced in ATLL patients compared to healthy individuals. IDO was strongly expressed at tissue level as well.[34] Lindström *et al*. determined activity and

expression of IDO for chronic lymphocytic leukaemia (CLL) in 49 patients. Enhanced activity of IDO was observed in the CLL patients as compared to control, but in peripheral blood mononuclear cells mostly representing the malignant B cells, the gene expression of IDO1 and IDO2 was reduced. They found that IDO activity in CLL patients is associated with disease progression, even though it originates from cells other than malignant B cells.[35]

A comprehensive study conducted to investigate the IDO1 expression and function in 21 children with acute myeloid leukaemia (AML), [10 AML, 9 B-cell precursor (BCP)-ALL, one infant acute leukaemia with MLL rearrangement and 1 T-cell ALL] and in one patient with Ph+ chronic myeloid leukaemia. IDO activity was measured by reverse phase-HPLC. They found functional IDO1 expression in blast cells from of childhood AML subset, but not those from BCP-ALL or T-cell ALL. STAT3 inhibitors may effectively disrupt IDO1 expression by AML cells, thus in favour of anti-leukaemia immune responses tipping T helper type 1/2 (Th1/Th2) equilibrium.[36] Nakamura *et al*. explored the therapeutic potential of IDO inhibitor, D-1MT with cyclophosphamide (CY) using an IDO-positive B-cell lymphoma mouse model. D-1MT in

Table 3: Indoleamine 2,3-dioxygenase involvement in haematological malignancies

Year	Investigator	Description
2009	Hoshi *et al*.[34]	IDO is highly expressed in adult T-cell leukaemia/lymphoma. IDO-initiating L-tryptophan catabolism changes with chemotherapy
2012	Lindström *et al*.[35]	High IDO activity was observed in chronic lymphocytic leukaemia patients as compared to control. Increased IDO activity may affect disease progression
2012	Folgiero *et al*.[36]	IDO1 is expressed by a subset of childhood acute myeloid leukaemia and restrains IFN-γ production by T-cells
2013	Nakamura *et al*.[37]	IDO inhibitor in combination with cyclophosphamide is an effective treatment for IDO-positive lymphoma in a mouse model. IDO inhibition might offer a favourable treatment strategy for lymphoma
2014	Liu *et al*.[38]	IDO1 upregulation in non-Hodgkin lymphoma tissues could induce local immune tolerance by infiltration of FoxP3+T-regs in the tumour microenvironment. This could be a novel mechanism of immune escape
2014	Choe *et al*.[39]	IDO is associated with the adverse clinical outcomes in (HL). IDO is an independent prognostic factor in nodular sclerosis HL
2014	Folgiero *et al*.[40]	IDO1 expression by leukaemia blasts negatively affects the prognosis of childhood (AML). IDO can be targeted, in adjunct to current chemotherapy strategies, to improve the clinical outcome of children with AML
2016	Mansour *et al*.[41]	High IDO expression in mesenchymal stem cells and increased levels of T-regs play pivotal role in the pathogenesis of AML

IDO: Indoleamine 2,3-dioxygenase, HL: Hodgkin lymphoma, AML: Acute myeloid leukaemia, IFN-γ: Interferon gamma

combination with CY was recommended by them as an effective IDO-positive lymphoma treatment. These findings suggest that inhibition of IDO might offer a therapeutic approach for lymphoma.[37]

A recently published study demonstrated the role of IDO in non-Hodgkin lymphoma (NHL). They identified IDO1 upregulation in NHL tissues. They suggested that IDO has a critical role in immune escape mechanism in NHL.[38] IDO is not only involved in the non-HL pathogenesis but also the HL. A study conducted by Choe et al. described IDO role in the HL microenvironment. They identified HL tissues with IDO positive cells. This study was the first of its kind in defining IDO as a principle immune-modulator and its involvement to adverse clinical outcomes of HL.[39] A research published by Folgiero et al., in 2014, which was the continuation of his previous work published in 2012, suggested expression of IDO1 by leukaemia blasts adversely affects childhood AML prognosis. The 8-year event-free survival from a clinical standpoint was markedly worse in IDO-expressing children as compared to non-expressing ones. Chemotherapeutic agents in combination with IDO inhibitors were proposed by them to improve the clinical outcomes in the children with AML.[40] Another study on AML revealed that elevated level of T-regs has relationship with enhanced expression of IDO in mesenchymal stem cells which, in turn, responsible for immunosuppression in the tumour microenvironment. IDO has the main role in the pathogenesis of AML.[41]

IDO in Prostate Cancer

Prostate cancer is the most commonly diagnosed malignancy and a leading cause of mortality worldwide.[42] Overexpression of IDO gene was observed in the prostate cancer patients [Table 4]. Feder-Mengus et al. evaluated the expression of IDO and few other genes in benign prostatic hyperplasia (BPH) and prostate-specific antigen (PCA) tissues in 76 patients. IDO gene expression was quantitatively higher ($P = 0.00001$) and more repeatedly detectable ($P = 0.00007$) in PCA tissues in comparison with BPH. In serum analysis of these patients indicated an association between kynurenine/tryptophan ratio and IDO gene expression.[43] The same kind of results identified by Provenzano et al. that IDO has potential to use as biomarker of malignant transformation in prostate cancers and warranted further research in PCA patients.[44]

Gray et al., in 2009, identified the upregulation of tumour IDO and transforming growth factor-beta in more advanced prostate cancer. They proposed that immunotherapy clinical trials in prostate cancer patients will be more fruitful if conducted in less advanced disease.[45] Matos et al. pointed out the role of IDO in prostate cancer and suggested that IDO inhibition has clinical implication in prostate cancer.[46]

IDO in Pancreatic Cancer

IDO upregulation is associated with an increased number of T-regs in metastatic pancreatic ductal adenocarcinoma cells.[47] T-regs are key mediators of peripheral tolerance and have immunosuppressive activity.[48] Low numbers of T-regs in pancreatic tumours were found to have a markedly better survival in comparison with high T-regs number in tumours.[49] Kobayashi et al. investigated the localization and prevalence of CD8+ lymphocytes, IDO expression and FOXP3+ T-regs in intraductal papillary mucinous neoplasms (IPMNs) by immunohistochemistry in 39 cases. They observed IDO expression in the tumour

Table 4: Indoleamine 2,3-dioxygenase involvement in prostate cancer

Year	Investigator	Description
2008	Feder-Mengus et al.[43]	High expression of IDO gene was explicitly detectable in (PCA)
2008	Provenzano et al.[44]	IDO gene expression, recurrently detectable in PCA and associated with (AMACR) expression, seems to qualify as a marker of malignant transformation in prostate cancers
2009	Gray et al.[45]	IDO, TGF-β upregulation and induction of T-regs in an immunosuppressive intratumoral cytokine milieu identified in more advanced prostate cancer
2016	Matos et al.[46]	IDO is produced constitutively by PC3 (human prostate cancer cell line) cells and its expression increase when the cells are exposed to IFN-γ

IDO: Indoleamine 2,3-dioxygenase, PCA: Prostate-specific antigen, AMACR: Alpha-methylacyl-CoA racemace, TGF-β: Transforming growth factor beta

Table 5: Indoleamine 2,3-dioxygenase involvement in pancreatic cancer

Year	Investigator	Description
2008	Witkiewicz et al.[47]	IDO inhibition in (PDA) patients can be useful to enhance immunotherapeutic strategies
2010	Kobayashi et al.[50]	IDO expression in the tumor is one of the late-stage phenomena of multistage carcinogenesis of (IPMNs)
2013	Ikemoto et al.[51]	IDO-positive cells had a significantly higher recurrence than those with less IDO-positive cells. Pathological aggressiveness of IPMNs is associated with IDO induced FOXP3 + T-regs
2014	Peng et al.[53]	Elevation of (MMP-9) and IDO-induced by pancreatic cancer cells mediates (NK) cell dysfunction. MMP-9 and IDO facilitate pancreatic cancer cells to evade immunosurveillance

PDA: Pancreatic ductal adenocarcinoma, IDO: Indoleamine 2,3-dioxygenase, IPMNs: Intraductal papillary mucinous neoplasms, MMP-9: Matrix metallopeptidase 9, NK: Natural killer

was positively correlated with the prevalence of T-regs in IPMNs.[50] Another study conducted by Ikemoto et al. to evaluate weather IDO and FOXP3+ T-regs interaction play a role in IPMN in pathological aggressiveness. They observed that the IDO-positive patient cells had a considerably higher recurrence than those with less IDO-positive cells. The aggressiveness of IPMNs is correlated with the involvement of FOXP3+ cells. IDO-positive cells in IPMNs can induce an increase in the FOXP3+ cells.[51] Natural Killer (NK) cells are key components in the innate immune system and are capable of destroying the cancer cells directly. Dysfunction of NK cells has been investigated in pancreatic cancer.[52] Induction of IDO by pancreatic cancer cells promotes NK cell dysfunction.[53] IDO helps pancreatic cancer cells to evade immunosurveillance[53] [Table 5].

IDO as an Immunotherapeutic Target

IDO is involved in immune system regulation. IDO upregulation is associated with poor prognosis in various cancers[20,30,34,35,39,41,43,51] but few studies suggested that increased expression of IDO was linked with favourable prognosis.[19,46] Further studies are required in view of the contradictory findings, to comprehend this complex role of IDO in various cancers. At present, in clinical stage, three IDO inhibitors are in commercial production as immunotherapeutic agents in breast cancer treatment. These include indoximod (NLG2101) developed by NewLink Genetics™,[54] INCB024360 developed by Incyte™[55,56] and NLG919 licensed to Genentech™.[57] Two therapies (NCT01042535 and NCT01792050) have been exclusively designed to treat HER2-positive breast cancer in combination with AD.p53 DC vaccine and docetaxel, respectively.[58] Another immunotherapy is available for patients with metastatic pancreatic cancer

(NCT02077881).[59,60] NCT01560923 is currently approved for the individuals with refractory metastatic prostate carcinoma.[61,62] IDO-2 is a recently discovered IDO isoform.[63] Future studies on the role of IDO-2 should be focused as well in cancer. Therapeutic implications of IDO have significant outcomes.

Evidence Acquisition

The search strategy used the following keywords: 'Immunotherapy' or 'IDO' or 'Breast cancer' or 'Colon cancer' or 'Haematological malignancies' or 'Prostate cancer' or 'Pancreatic cancer.' Three electronic databases (PubMed/MEDLINE, SCOPUS and GOOGLE SCHOLAR) were searched for articles published between 2008 and 2017. The most relevant articles were extracted from the literature.

Conflict of Interest

The authors declare that they have no conflict of interest.

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