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REVIEW

Indoleamine-2,3 dioxygenase: a fate-changer of the tumor microenvironment

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Abstract

Indoleamine-2,3 dioxygenase is a rate-limiting enzyme in the tryptophan catabolism in kynurenine pathways that has an immunosuppressive effect and supports cancer cells to evade the immune system in different cancer types. Diverse cytokines and pathways upregulate the production of indoleamine-2,3 dioxygenase enzymes in the tumor microenvironment and cause more production and activity of this enzyme. Ultimately, this situation results in anti-tumor immune suppression which is in favor of tumor growth. Several inhibitors such as 1-methyl-tryptophan have been introduced for indoleamine-2,3 dioxygenase enzyme and some of them are widely utilized in pre-clinical and clinical trials. Importantly at the molecular level, indoleamine-2,3 dioxygenase is positioned in a series of intricate signaling and molecular networks. Here, the main objective is to provide a focused view of indoleamine-2,3 dioxygenase enhancer pathways and propose further studies to cover the gap in available information on the function of indoleamine-2,3 dioxygenase enzyme in the tumor microenvironment.

Keywords IDO · Kynurenine · IDO inhibitor · Immunosuppression · Cancer · Tumor microenvironment

Abbreviations

TRP	Tryptophan
IDO	Indoleamine-2,3 dioxygenase
Kyn	Kynurenine
AhR	Aryl hydrocarbon receptor
TME	Tumor microenvironment
NK cells	Natural killer cells
DC	Dendritic cells
Treg	Regulatory T
MDSCs	Myeloid-derived suppressor cells
IL	Interleukin
TGF-β	Transforming growth factor-beta
EVT	Extravillous trophoblasts
TAMs	Tumor-associated macrophages
pDCs	Plasmacytoid dendritic cells
inf-DC	Inflammatory DC
cDC	Conventional DC
APCs	Antigen presenting cells
CTLA-4	Cytotoxic T-lymphocyte–associated antigen 4
TDO	Tryptophan 2,3 dioxygenase
K_m	Michaelis–Menten kinetics
NAD^+	nicotinamide adenine dinucleotide
TPH1	Tryptophan Hydroxylase 1
TPH2	Tryptophan Hydroxylase 2
1-MT	1-methyl-tryptophan
D-1MT	1-methyl-D-tryptophan
L-1MT	1-methyl-L-tryptophan
JAK	Janus kinase
STAT	Signal transducer and activator of transcription
NF-κB	Nuclear factor-κB
IFN-γ	Interferon gamma
TCGA	Cancer Genome Atlas
TLR4/MyD88	Toll-like receptor-4-myeloid differentiation primary response 88

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TNFα	Tumour Necrosis Factorα
VEGF	Vascular endothelial growth factor
PD-1	Programmed death-1
BTLA	T lymphocyte attenuator
GBP1	Guanylate-binding protein 1
PSA	Prostate specifc antigen
COX2	Cyclooxygenase-2
FoxP3	Forkhead box P3
PI3K	Phosphoinositide 3 kinase
Akt	Protein kinase B
APC	Antigen-presenting cells
RelB	v-rel reticuloendotheliosis viral oncogene homolog B
Etv4	ETS Variant Transcription Factor 4
KIT	Tyrosine-protein kinase
LPS	Llipopolysaccharide
PGE2	Prostaglandin E2
MAPKs	Mitogen activated protein kinases
IRF1	Interferon regulatory factor 1
GAF	IFN-gamma activated factor
Bin1	Bridging Integrator 1
Etv4	ETS Variant Transcription Factor 4
KIT	Tyrosine-protein kinase

Introduction

Cancer is one of the highest causes of death and an important obstacle to improving life expectancy. In 2020, the coronavirus disease (COVID-19) pandemic caused a reduction in diagnosis and treatment services for cancer because of fear of COVID-19 exposure and diminished in-person health services [1]. Consequently, merely in the united states, new cases and deaths number to cancer are estimated at 2,370,000 and 640,000, respectively, in 2022 [2]. Estimating the consequences of the COVID-19 pandemic on cancer diagnosis and treatment at the world population level may demand some decades due to the delay in releasing the population big data in healthcare.

The classic definition suggests that mutations in different genes, such as LEP, TP53, and NeuroD1, are the key role players in chronic diseases such as diabetes and cancer [3–5]. However, nowadays it is demonstrated that most cancer types are not only genetic disorders but also metabolic disorders. Among many metabolic pathways, tryptophan (TRP) metabolism is one of the most vital and fundamental biological processes for all cell types including cancer cells [6]. Indeed, TRP is an aromatic and essential amino acid that mammals are not able to synthesize it, therefore, dietary sources of TRP is required [7]. Indeed, TRP undergoes complex metabolic routes, resulting in the production of many types of signaling molecules [8]. Due to this importance, during the last two decades, TRP metabolism received significant attention in pre-clinical and clinical studies.

Indoleamine-2,3 dioxygenase (IDO) is the first rate-limiting step during the catabolism of TRP [9]. It is coded by the IDO gene which in the human genome, is located on chromosome 8p12. The IDO gene family contains IDO1 and IDO2, but IDO2 in comparison to IDO1 has a weaker performance. Thus, IDO2 is considered with a less efficiency on the TRP metabolism [10]. The IDO contains 407 amino acids heme-containing and is a cytoplasmic protein [9]. IDO initiates its biological influences by metabolizing TRP into kynurenine (Kyn). Kyn causes to decrease in antitumor immunity of T cells via aryl hydrocarbon receptor (AhR) signaling. Altogether, the IDO is well known for its immunosuppressive function and indirect action in favor of tumor microenvironment (TME) growth [11].

The tumor has a complex and dynamic microenvironment that usually consists of different cell types, such as cancer cells, stromal cells, endothelial cells, and immune cells. Tumor-infiltrating immune cells can be classified into two main groups. One group has the tumor-antagonizing characteristic that contains effector T cells, natural killer (NK) cells, dendritic cells (DCs), M1-polarized macrophages, and N1-polarized neutrophils. And the other group is tumor-promoting cells namely, regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs) [12]. In addition to immune cells, cytokines such as interleukin (IL) 6, IL-10, and Transforming growth factor-beta (TGF-β) are essential role players in the TME that cause chronic inflammatory state and immunosuppression [13].

In this review, we focus on the characteristics of the IDO and the pathways that induce the production of IDO in the TME. In addition, the gap in information regarding single-cell RNA-seq analysis and IDO function in the TME is addressed.

Characteristics of IDO enzyme

In 1936, Kotake and Masayama discovered an enzyme in the liver of mammals and named it tryptophan-oxygenase, which changed later to tryptophan-dioxygenase [14]. During evolution, the main features of the IDO enzyme have been conserved in vertebrates. Pioneering investigations unveiled that IDO was highly expressed in placenta tissue. The function of this enzyme is vital for protecting embryos from the maternal immune system [15]. In the human placenta, IDO is express in the glandular epithelium in the decidua [16]. One of the main function of the IDO is to maintain the tolerance in placenta [17]. In placenta, a specific cell type which is called extravillous trophoblasts (EVT) invade the uterine implantation site in order to remodeling and adapting

the blood flow for feed fetus. Thereby, EVT come across with a direct contact with maternal cells [18]. EVT significantly express IDO and the activity of IDO is an important role player in order to suppress the proliferation of the T cells. Hence, the function of IDO protects the fetal tissue against the rejection by the maternal immune system and consequently, reduces the chance of abortion [17]. Since, the function of the IDO results in supressing the appropriate function of T cells, tumor cells use IDO as an advantage. Indeed, tumor cells express IDO and support IDO expression in other cell types in the TME in order to reduce the capacity of anti-tumor immunity [19].

Fundamentally, the characteristics of IDO1, IDO2, and tryptophan 2,3 dioxygenase (TDO) enzymes are different from each other. From an enzymatic perspective, IDO1 is a monomeric enzyme that is located in the majority of the tissues and is responsible for the regulatory role of immune responses. Indeed, the low Michaelis–Menten kinetics (K_m) rate of IDO1 allows it to efficiently deplete TRP in the local microenvironment [20]. Whereas IDO2 is not as effective as IDO1, and the capacity of IDO2 for TRP degradation is not considered high. Indeed, the K_m of the IDO2 enzyme is almost 100-fold higher than IDO1 and TDO in the physiological concentration of TRP. Specifically, in humans and mice, the K_m of IDO2 is approximately 6.8 and 12 mM, respectively [20]. In comparison to IDO, less is known about the characteristics of TDO. Similar to IDO, TDO is a heme-containing enzyme and its K_m is about 0.135 mM [21, 22]. In addition, IDO1, IDO2, and TDO enzymes have different expression levels in various tissues. The majority of TDO is localized exclusively in the liver, whereas IDO1 is usually detected in other organs such as the placenta, peripheral nervous system, and central nervous systems [23]. Although much less is known about IDO2, it is suggested that it may be expressed at a lower level in the liver, testis, and thyroid [20]. Finally, these three enzymes have different expression levels in cancer types. In various human cancers, IDO1 and, less frequently, TDO are expressed and cause tumor immune resistance features. Interestingly, IDO2 is not expressed so often in human tumors [20].

IDO in kynurenine pathway and its inhibitors

TRP is an essential amino acid for humans and in different physiological conditions it is able to enter into four different biochemical pathways namely, the melatonin synthesis pathway, indole pathway, protein synthesis, and Kyn pathway [24]. The indole pathway appears merely in the intestinal flora of mammals. It is the source of indole products such as indole-3-acetic acid and indole-3-carboxaldehyde which are involved in intestinal immunity regulation via AhR [25]. The Kyn pathway absorbs the majority of available TRP. In most organs, around 95% of TRP is converted into N-Formylkynurenine by IDO1, IDO2, or TDO [26]. Subsequently, N-Formylkynurenine is converted to Kyn by the formamidase enzyme [27]. As an endogenous system, the Kyn pathway contains immunosuppressive characteristics that participate in inflammation and long-term immune tolerance control [28]. Also, this pathway produces important metabolites such as quinolinic acid which ultimately end up in nicotinamide adenine dinucleotide (NAD^+) production via the Preiss-Handler pathway and 2-Aminomuconic acid which ends up in glycolysis and benzoate degradation processes [29, 30]. Interestingly, the metabolism of TRP in the brain is different than in other organs. Approximately 1% of dietary TRP consumption is related to the production of Serotonin, N-acetylserotonin, and melatonin in the brain [31]. In this complex organ, during the first step of serotonin synthesis, which is the rate-limiting step of serotonin synthesis, TRP is converted to 5-hydroxytryptophan by the function of the tryptophan hydroxylase 1 (TPH1) and 2 (TPH2) enzymes. In the second step, 5-hydroxytryptophan is converted to serotonin by reacting with the aromatic L-amino acid decarboxylase enzyme (DOPA decarboxylase). Importantly, in the brain, the available concentration of TRP is the regulator for the activity of the TPH1 and TPH2 enzymes (Fig. 1) [31, 32].

Among different IDO inhibitors such as BMS-986,205, INCB024360 (Epacadostat), NLG919 (Navoximod), and Norharmane; 1-methyl-tryptophan (1-MT) has been utilized in many studies [33]. 1-MT induces the rejection of fetuses capable of beginning the maternal immune response. Historically, utilizing 1-MT indicated the importance and extraordinary capacity of the IDO1 enzyme in the immune system's tolerance [15, 34]. The importance of IDO is not limited only to preclinical studies, several clinical trials have started to investigate the role of IDO inhibitors in different cancer types (Table 1). 1-methyl-D-tryptophan (D-1MT) and 1-methyl-L-tryptophan (L-1MT) are two stereoisomers of 1-MT that provide different effects on blocking IDO depending on the cell type [35]. It was noted that L-1MT abolishes IDO1 activity, whereas D-1MT nearly exclusively inhibits IDO2 [36]. Interestingly, the L isomer has higher biochemical activity than the D isomer [37].

Last but not least, salinomycin (an antibacterial and coccidiostat ionophore therapeutic drug) decreases the expression levels of IDO1 and IDO2. It represses the Janus kinase/Signal transducer and activator of transcription (JAK/STAT) and nuclear factor-κB (NF-κB) pathways with the collaboration of interferon-gamma (IFNγ). It is suggested that salinomycin diminishes Kyn production and consequently acts against tumor favor [38].

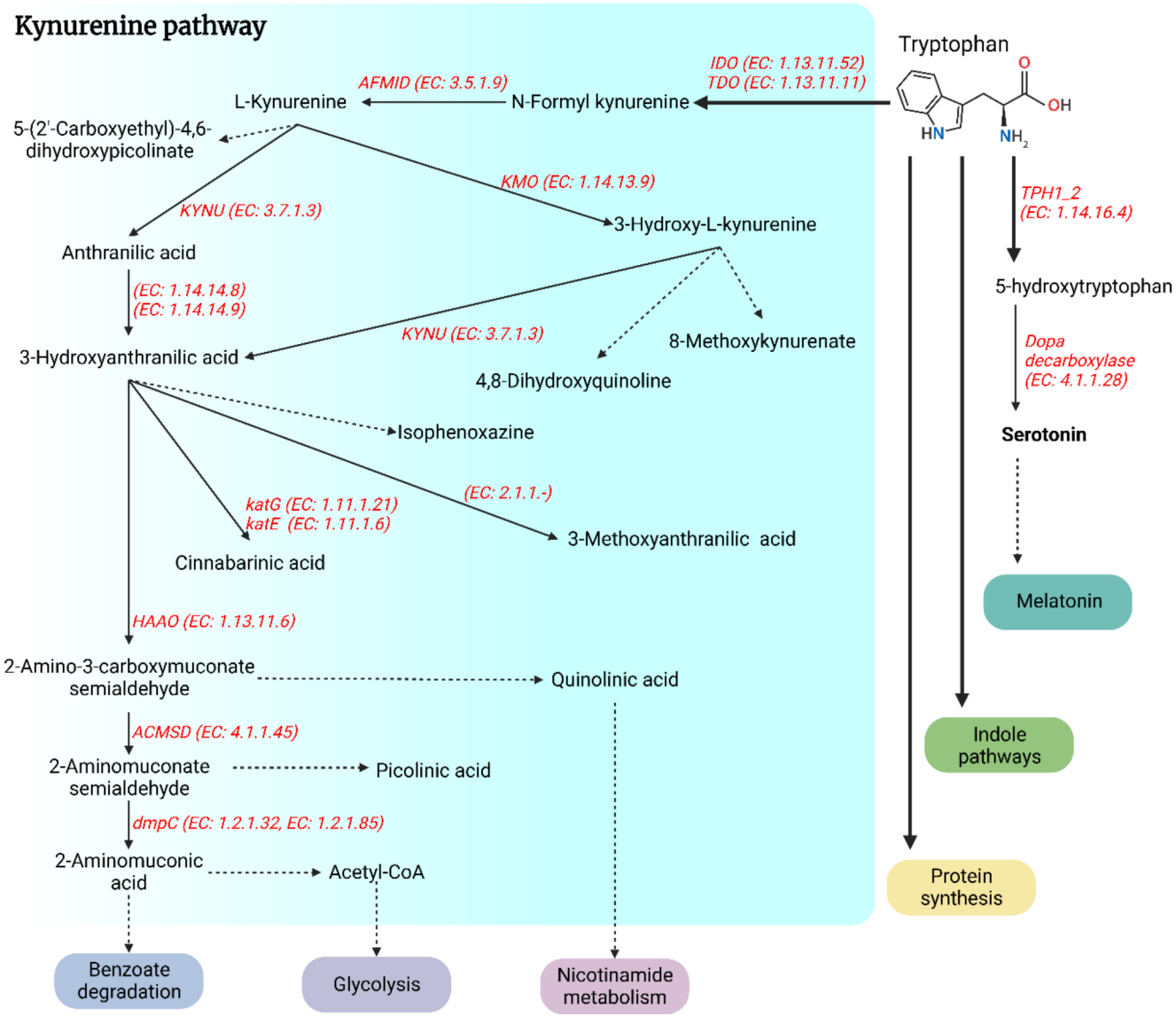

Fig. 1 Summary of the kynurenine pathway of tryptophan metabolism. The solid arrows represent one enzymatic step process and the dash arrows represent more than one enzymatic or non-enzymatic step. The Enzyme Commission number (EC) and symbols of enzymes are shown in red and italics

IDO in immune cells

The TME contains a wide range of immune cells generally including macrophages, DCs, T cells, MDSCs, mast cells, and NK cells [39]. Macrophages contain two main subtypes namely, M1 and M2 macrophages. While M1 macrophage has tumor-resistant characteristics, M2 macrophage has tumor-promoting capabilities. M2 macrophages, generally assumed tumor-associated macrophages (TAMs). TAMs are considered as the major inflammatory cells in TME [40]. TAMs have tumor supporting characteristics by modifying angiogenesis, extracellular matrix and chronic inflammation. Also, they support immune suppression processes via various signaling pathways such as NF-κB and Jak-STAT3 [39]. It is shown that IDO plays an important role in macrophage differentiation and induces macrophages to M2 sub type [41].

DCs are vital role players in TME which contain different subtypes with anti-tumor or tumorigenesis characteristics. It is illustrated that plasmacytoid dendritic cells (pDCs) are involved in tumorigenesis process, while, inflammatory DC (inf-DC) and conventional DC (cDC) have a controversial role in TME [42]. IDO by consuming the available TRP in TME cause to activation of DCs [43]. DCs themselves also are able to produce IDO during reaction to different immunogenic and tolerogenic molecules. Overall, IDO production in DCs can prevent a potent anti-tumor response [44].

Table 1 IDO inhibitors in clinical trials

R	IDO Inhibitor(s)	Phase	Cancer types	Drug testing in combination with	Status	clinicaltrials.gov Identifier
1	Indoximod	2	Metastatic breast cancer	Docetaxel Paclitaxel	Completed	NCT01792050
2	Epacadostat	2	Ovarian cancer/ Genitourinary (GU) tumors	Tamoxifen	Terminated	NCT01685255
3	Indoximod	1/2	Metastatic pancreatic adenocarcinoma; Metastatic pancreatic cancer	NabPaclitaxel; Gemcitabine	Completed	NCT02077881
4	SHR9146	1	Solid tumor; Metastatic cancer; Neoplasm malignant	SHR-1210 Apatinib	Unknown	NCT03491631
5	BMS- 986,205	2	Endometrial adenocarcinoma; Endometrial carcinosarcoma	BMS- 986,205 Nivolumab	Active, not recruiting	NCT04106414
6	Indoximod	1/2	Glioblastoma multiforme; Glioma; Gliosarcoma; Malignant brain tumor	Temozolomide Bevacizumab	Completed	NCT02052648
7	Indoximod	1	Non-small cell lung cancer; Progression of non-small cell lung cancer; Non-small cell lung cancer recurrent	Docetaxel Tergenpumatucel-L	Terminated	NCT02460367
8	1-methyl-Dtryptophan	1	Breast cancer; Lung cancer; Melanoma; Pancreatic cancer; Solid tumors	-	Terminated	NCT00739609
9	INCB024360	1	Ovarian cancer; Fallopian tube carcinoma; Primary peritoneal carcinoma	Fludarabine; Cyclophosphamide	Completed	NCT02118285
10	Epacadostat	1/2	Breast cancer female; Breast neoplasm female	INCMGA00012; Low dose Cyclophosphamide; Interferon inoculation	Recruiting	NCT03328026
11	Epacadostat	2	Gastrointestinal stromal tumors	Pembrolizumab	Completed	NCT03291054
12	KHK2455	1	Urothelial carcinoma	Avelumab	Active, not recruiting	NCT03915405
13	LY3381916	1	Solid tumor; Non small cell lung cancer; Renal cell carcinoma; Triple negative breast cancer	LY3300054	Terminated	NCT03343613
14	Indoximod	1	Ependymoma; Medulloblastoma; Glioblastoma; Primitive; Neuroectoderma	Cyclophosphamide; Etoposide; Ibrutinib	Recruiting	NCT05106296
15	Epacadostat	1/2	Solid Tumor	Oxaliplatin; Leucovorin; 5-Fluorouracil; Gemcitabine; nab-Paclitaxel; Carboplatin; Paclitaxel; Pemetrexed; Cyclophosphamide; Cisplatin; platinum agents	Completed	NCT03085914
16	Epacadostat	1/2	Solid Tumors	Nivolumab; Ipilimumab; Lirilumab	Terminated	NCT03347123
17	Epacadostat	1/2	Recurrent fallopian tube cancer; Recurrent ovarian epithelial cancer; Recurrent primary peritoneal cavity cancer; Stage IA fallopian tube cancer; Stage IA ovarian epithelial cancer; Stage IA primary peritoneal cavity cancer; Stage IB fallopian tube cancer; Stage IB ovarian epithelial cancer; Stage IB primary peritoneal cavity cancer; Stage IC fallopian tube cancer; and 23 more	ALVAC(2)-NYESO-1 (M)/TRICOM vaccine	Withdrawn	NCT01982487
18	NLG802	1	Solid Tumor	-	Completed	NCT03164603
19	Epacadostat	1/2	Fallopian tube carcinoma; Ovarian carcinoma; Primary peritoneal carcinoma	Poly ICLC	Completed	NCT02166905

Table 1 (continued)

R	IDO Inhibitor(s)	Phase	Cancer types	Drug testing in combination with	Status	clinicaltrials.gov Identifier
20	Indoximod	1/2	Metastatic Melanoma; Stage III Melanoma; Stage IV Melanoma	Pembrolizumab; Nivolumab; Ipilimumab	Completed	NCT02073123
21	-	2	Endometrium cancer	Celecoxib 200 mg capsule	Unknown	NCT03896113
22	GDC-0919	1	Solid Tumor	-	Completed	NCT02048709
23	Indoximod	1	Glioblastoma multiforme; Glioma; Gliosarcoma; Malignant brain tumor; Ependymoma; Medulloblastoma; Diffuse intrinsic pontine glioma; Primary CNS tumor	Etoposide; Cyclophosphamide; Temozolomide	Completed	NCT02502708
24	HTI-1090	1	Advanced Solid Tumors	-	Completed	NCT03208959
25	Epacadostat	1	Stage III fallopian tube cancer AJCC v7; Stage III ovarian cancer AJCC v6 and v7; Stage III primary peritoneal cancer AJCC v7; Stage IIIA fallopian tube cancer AJCC v7; Stage IIIA ovarian cancer AJCC v6 and v7; Stage IIIA primary peritoneal cancer AJCC v7; Stage IIIB fallopian tube cancer AJCC v7; Stage IIIB ovarian cancer AJCC v6 and v7; Stage IIIB primary peritoneal cancer AJCC v7; Stage IIIC fallopian tube cancer AJCC v7; and 5 more	-	Active, not recruiting	NCT02042430
26	BMS-986,205	1/2	Metastatic hepatocellular carcinoma; Stage III hepatocellular carcinoma AJCC v8; Stage IIIA hepatocellular carcinoma AJCC v8; Stage IIIB hepatocellular carcinoma AJCC v8, Stage IV hepatocellular carcinoma AJCC v8; Stage IVA hepatocellular carcinoma AJCC v8; Stage IVB hepatocellular carcinoma AJCC v8; Unresectable hepatocellular carcinoma	Nivolumab	Active, not recruiting	NCT03695250
27	DN1406131	1	Advanced solid tumors	-	Unknown status	NCT03641794
28	BMS-986,205	1/2	Advanced cancer	-	Recruiting	NCT03459222
29	Epacadostat	2	ATM gene mutation; Deleterious BRCA1 gene Mutation; Deleterious BRCA2 gene Mutation; Homologous recombination Deficiency; Pancreatic ductal Adenocarcinoma; Stage II pancreatic cancer AJCC v8; Stage IIA pancreatic cancer AJCC v8; Stage IIB pancreatic cancer AJCC v8; Stage III pancreatic cancer AJCC v8; Stage IV pancreatic cancer AJCC v8	Pembrolizumab	Withdrawn	NCT03432676
30	BMS-986,205	2	Lip; Oral Cavity Squamous Cell Carcinoma; Pharynx; Larynx; Squamous cell carcinoma	Nivolumab	Recruiting	NCT03854032
31	Epacadostat	2	Mucosal melanoma; Recurrent melanoma; Recurrent uveal melanoma; Stage IIIA skin melanoma; Stage IIIA uveal melanoma; Stage IIIB skin melanoma; Stage IIIB uveal melanoma; Stage IIIC skin melanoma; Stage IIIC uveal melanoma; Stage IV skin melanoma; Stage IV uve	MELITAC 12.1 Peptide Vaccine	Completed	NCT01961115
32	Epacadostat	2	Sarcoma	Pembrolizumab	Active, not recruiting	NCT03414229

Table 1 (continued)

R	IDO Inhibitor(s)	Phase	Cancer types	Drug testing in combination with	Status	clinicaltrials.gov Identifier
33	INCB024360	1	Glioblastoma; Glioblastoma multiforme	Ipilimumab; Anti-GITR monoclonal antibody MK-4166; Nivolumab	Terminated	NCT03707457
34	BMS-986,205	1	Glioblastoma	Nivolumab; Temozolomide	Recruiting	NCT04047706
35	Epacadostat	2	Myelodysplastic syndromes	-	Completed	NCT01822691

Despite anti-tumor immune function by T cells, they can also cause immune tolerance [45]. IDO via different signalings such as Fas-mediated and Vav1 signalings can suppress T cells. Indeed, the Vav1 signaling pathway is one of the adjusters of T cell homeostasis [46]. Interestingly, it is revealed that IDO specific $CD8^+$ T cells can determine IDO^+ suppressive cells such as IDO-expressing DCs and destroy them. Thereby, IDO specific $CD8^+$ T cells are able to enhance T cell immunity versus tumor-associated antigen [47]. Tregs increase IDO production in antigen presenting cells (APCs) through cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4)/B7 signaling in the lymph nodes that are draining tumor sites [48].

Gradually by growing the TME immunosuppressive cells such as MDSCs and Treg cells begin to prohibit the proliferation and activity of cytotoxic T cells. MDSCs are a heterogeneous population that repress the function of T and NK cells to assist development of tumor, pre-metastatic niche, and immunotherapy resistance [49]. By the activity of IDO, MDSCs cause and preserve of immune tolerance and tumor immune escape by boosting the function of Treg cells [50].

Mostly, it is still unknown whether mast cells and NK cells are able to produce IDO in human tumor microenvironments. Canine mast cell tumour cells express IDO in order to control the levels of TRP and KYN [51]. Also, it is reported that cell to cell contact of mast cells and monocyte derived DCs significantly expand the expression of IDO in monocyte derived DCs. Some studies showed that IDO expression in cancer associated fibroblasts suppresses NK cell activity [48]. Recently, it is demonstrated that the activity of IDO can interrupt NK cells function by reducing the NKG2D ligand in non-small cell lung cancer [52]. Although many studies dedicated to understand the function of IDO in the tumor microenvironment, many effects of the function IDO on immune cells and their subtypes have yet to be well understood.

Finally, IDO via toll-like receptor-4-myeloid differentiation primary response 88 (TLR4/MyD88) pathways controls the activation of NF-κB and the presence of proinflammatory cytokines, such as IL-1β, IL-6, TNFα (Tumour Necrosis Factor α), IL-23, and IL-17 A [53].

IDO expresses in various cancer types

IDO1 in cancer types

The IDO1 expression is significantly high in some cancer types, such as triple-negative breast cancer, and prostate cancer [54–56]. In bladder cancer, microRNA-153 via inhibiting IL-6/STAT3/VEGF (Vascular endothelial growth factor) signaling targets the IDO1 expression and, consequently, reduces the cancer progression [57]. In addition, short hairpin RNA blocks the IDO1 function and leads to reducing the progression of lung cancer. It reduces the IL-2 and TNFα but raises the expression levels of inhibitory receptors Programmed death-1 (PD-1) as well as B-and-T-lymphocyte attenuator (BTLA) in T lymphocyte cells [58]. In addition, interferon-induced guanylate-binding protein 1 (GBP1) assists IDO1 in migrating to extracellular space and facilitates proliferation and metastasis. Intercepting the extracellular secretion of IDO1 reduces T cell exhaustion and consequently improves the anti-tumor impact of PD-1 inhibitors [59].

In prostate cancer, it is shown that high levels of IDO1 expression are related to low Gleason score and prostate-specific antigen (PSA) levels [60]. Also, in the E.G7-OVA tumor model, silencing the IDO1 gene in DC is illustrated as an effective therapeutic strategy [61]. In colorectal carcinoma and esophageal cancers, the higher expression levels of IDO1 and PD-L1 significantly correlated with a high mitotic index and poor survival rate [62, 63].

In cancer types such as breast and colorectal, IDO1 co-expressed with cyclooxygenase-2 (COX2) is a weak independent predictor for overall survival [64]. Also, in triple-negative breast cancer, the expression of IDO1 has an association with forkhead box P3 (FoxP3) positive cells [65]. Interestingly, it is suggested that IDO1 blocking might interrupt CTLA-4 signaling in breast cancer cells [66]. Specifically, in colorectal cancer IDO1 activates the

phosphoinositide 3 kinase/protein kinase B (PI3K/Akt) pathway that promotes tumor progression [67]. $CD8A^+/IDO1^+$ is introduced as a prognostic characteristic of overall survival and biomarker for colon cancer. Despite an elevated level of infiltrated CD8, a subtype of colon cancer with a high ratio of $CD8A^+/IDO1^+$ cells causes robust poor survival [68]. In addition, in pancreatic ductal adenocarcinoma, IDO inhibitors boost the cytotoxicity effect of γδ T cells on some of the pancreatic ductal adenocarcinoma cells but not all of them [69].

IDO2 and TDO in cancer types

By controlling IDO2 and producing more Kyn concentration, thyroid cancer cells suppress NK cell cytotoxicity. Indeed, the expression of NK receptors such as NKG2D and NKp46 are inhibited by STAT1 and STAT3 pathways, which regulate the promoter regions of these receptors [70]. In the squamous cell carcinomas subgroup, IDO2 and PD-L1 have a high co-expression. This expression level of IDO2 is a potential prognostic biomarker in non-small cell lung cancer [71]. IDO2 depletion in-vivo model with Lewis lung carcinoma declined tumor growth and modified tryptophan accumulation and Kyn reductions in TME; as a result, induced aggression of immune cells [72].

In comparison to IDO1 and IDO2, TDO is less known in TME. It is illustrated that the expression TDO is high in the SK-Mel-28 melanoma cell line, infiltrating polymorphonuclear leukocytes and endothelium in cervical TMEs [73, 74]. Combination therapy of PEG-KYNase and immune-checkpoint inhibitors remarkably decreased the level of Kyn by downregulating the IDO1 and TDO expression in the TMEs such as melanoma and breast cancer [75].

Enhancer pathways of IDO enzyme production

Different TMEs might express various levels of IDO and alterations in the expression of IDO in the immune cells cause modifications in the immune responses. Different pathways with positive feedback such as the AhR pathway can increase IDO production. Illustrated pathways in Fig. 2 are inductor mechanisms that support the expression of IDO.

Activated AhR increases the expression level of IDO and the IL-6 gene. Consequently, IL-6, via an autocrine manner by mediating SATA-3, maintains the expression level of the IDO (Fig. 2 – black arrows) [76]. Also, RelB (v-rel reticuloendotheliosis viral oncogene homolog B) is associated with AhR in the modulation of IDO concentration [77].

IDO expression is stimulated by proinflammatory cytokines such as TNFα, IFNγ, IL-1, lipopolysaccharide (LPS), and prostaglandin E2 (PGE2) [77–79]. IL-1 and TNFα together raise IFN-induced IDO activity [80]. IL-1 initiates a signaling cascade that causes the activation of NF-κB and mitogen activated protein kinases (MAPKs) and induces expression of interferon regulatory factor 1 (IRF1) [81, 82]. TNFα synergistically provokes *IDO* gene expression by STAT-1 and NFκB-dependent IRF1 signaling [83]. In addition, IFNγ phosphorylates STAT1 and induces the expression of IRF1 by mediating GAF (IFN-gamma activated factor), and consequently, the expression of IRF1 induces the expression of STAT1 and then IDO [84]. In DCs, the B7 receptor signaling causes production of IFN-γ by STAT1, p38 MAPK, and NF-κB (Fig. 2 – red, black-dashed and red dash arrows) [85].

Bridging integrator 1 (Bin1) was identified as an MYC-interacting protein with the ability to the tumor suppression function. In various cancers like primary breast cancer and metastatic prostate cancers, functional deletions in the BIN1 gene have been reported [86, 87]. The loss of BIN1 gene expression is correlated with raised NF-κB and STAT1-dependent expression of IDO [88]. Furthermore, studies on cancer cell lines revealed that IDO expression is connected to COX2 and prostaglandin E2 that act as autocrine signaling by the PGE2 receptor. This cascade stimulates IDO transcription via the PKC and PI3K signaling [21]. In cancer cells, activation of Etv4 (ETS Variant Transcription Factor 4) by CD117 (KIT - tyrosine-protein kinase) driven signaling induces IDO expression (Fig. 2 – green, gray, and purple arrows) [89].

TGF-β stimulates the expression of SHPs via Smad-dependent and PI3K-dependent pathways. Additionally, IDO recruits SHP1/SHP2 to stimulate the noncanonical NF-kB pathway by provoking phosphorylation of the kinase IKKα and p52-RelB. Subsequently, it stimulates the genes encoding IDO and TGF-β [90, 91]. Also, in DCs, LPS is an inductor of RelB which increases the IDO level (Fig. 2 – blue arrows) [77]. Importantly, T cells are considered as one of the protagonists of the first line against the cancer battle [92]. Many studies showed that IDO via different mechanisms manipulates T cells' function and causes anti-cancer immunosuppression, ultimately supporting TME. Furthermore, via increasing TGF-β production, IDO imposes modifications to the T cell populations [90].

Overall, IDO is a potential tool for supporting tumor cells to alter the TME in favor of tumor growth and progression. The expression ratio of IDO in the TME is adjusted by different mechanisms within an intricate network. The IDO network is a potential area to investigations for new cancer therapy targets.

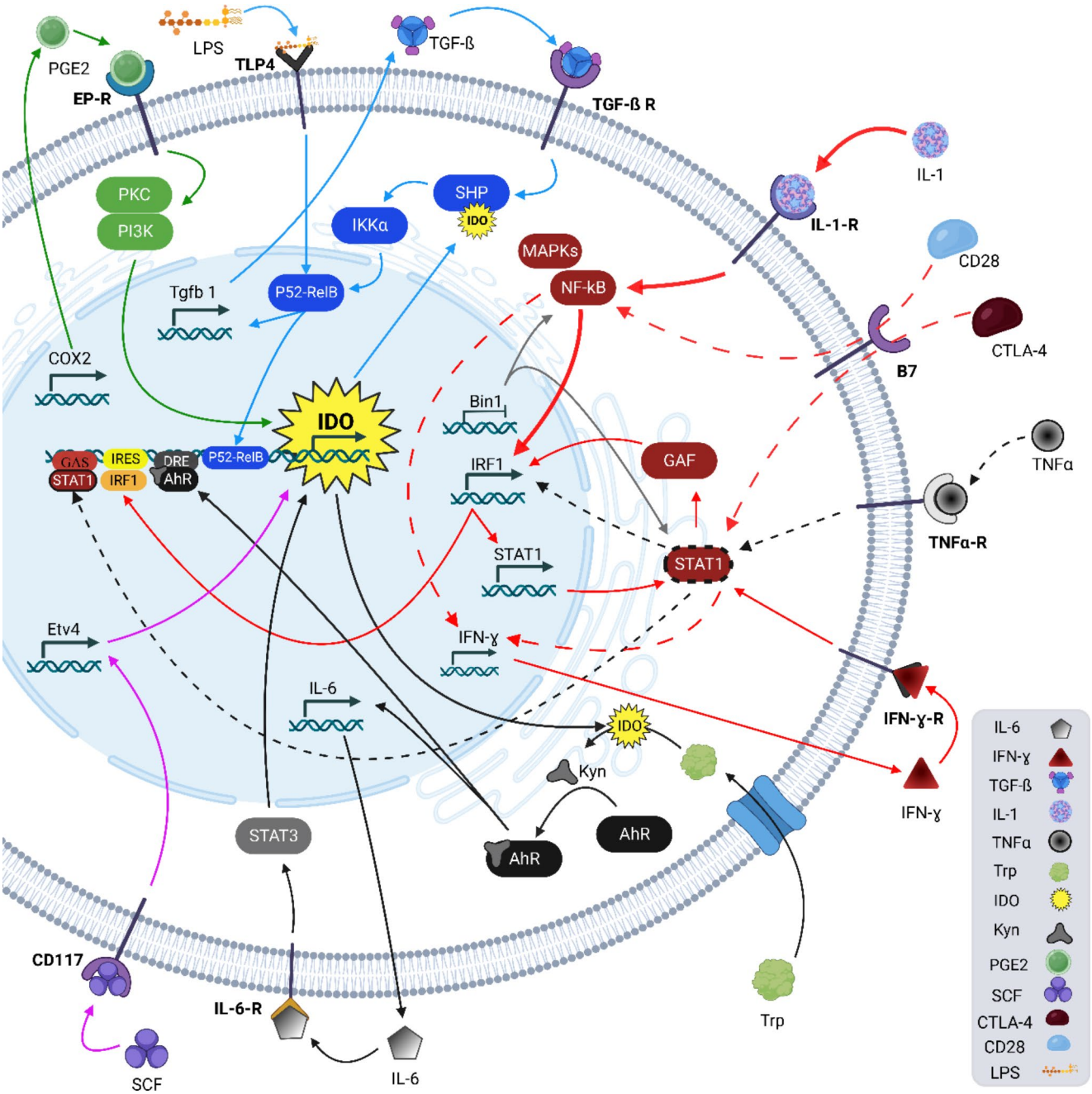

Fig. 2 Summary of IDO enzyme enhancer pathways. Each color or style of the arrow shows a group of related events

Conclusions and perspectives

The function of IDO is vital for immune tolerance in the placenta and other normal tissues, however, cancer cells also utilize the characteristics of the IDO to support their growth and survival. Indeed, IDO is located at the core of complicated signaling cascades, which can change the fate of tumor progression by manipulating different cell populations, such as T cells in the TME. In addition, IDO is becoming a hot topic in cancer therapy, hence, several IDO blockers such as Epacadostat, BMS986205, PF-06840003, Navoximod, Indoximod, NLG802, and LY3381916 entered to the clinical stage [93].

Immune checkpoints functionally are enormously important in both physiological and disease conditions, however in cancer types immune checkpoints might be associated with the immune escape phenomenon. For example, it is proposed that CTLA-4 signaling might support the immune escape of cancer cells [94]. In tumors with a high IDO expression, the AhR pathway is more active that causing

high resistance to immune checkpoint blockers [95]. The elevated expression and activity of IDO are connected to primary resistance to immunotherapy in patients with non-small cell lung cancer [96]. Also, IDO expression is linked to the progression of breast cancer and unsatisfactory response to neoadjuvant chemotherapy [97]. It is suggested that the co-expression of IDO and PD-L1 could be used to indicate a poor pathologic response after neoadjuvant chemoradiotherapy [98]. Despite efforts, many questions related to the function of IDO in the TME have yet to be well understood.

Basically, one of the challenging obstacles in cancer therapy is that while some patients respond to the treatments very well, others have relatively poor responses. The single-cell RNA sequencing technique in the recent decade has been remarkably advantageous in clarifying the reasons for this phenomenon. Although many studies have used single-cell RNA sequencing to study various aspects of cancer, there is a profound lack of single-cell RNA sequencing analysis on the role of IDO in TME. Using single-cell RNA sequencing analysis on different in-vivo and in-vitro models such as IDO knockout mouse models, IDO knockout cancer cells, or IDO overexpressed cancer cells will provide a wide overview of numerous gene expression alterations expressions. This information has a high potential to shed light many unknown aspects of the role of IDO in the TME as well as other immunological disorders.

Last but not least, the future perspective of immuno-oncology is dependent on the combination of immunotherapies. Since, most cell types in the TME are under the impact of signaling cascades of IDO, combining IDO inhibitors or IDO-linked cytokines such as TGF-β is a new approach in immuno-oncology. Specifically, it is not well understood whether inhibiting TGF-β potentialized the immune toxicities of other treatments [99]. Also, the concentration and timing of TGF-β blocking agents combined with other therapies are critical [100]. During the treatment of cancer with IDO and TGF-β inhibitors, the homeostatic functions of IDO and TGF-β should be considered precisely and not be compromised. Therefore, yet multifold doubts need to be clarified to utilize the therapeutic potential of IDO and TGF-β in clinical approaches.

Overall, IDO is a high-potential spot for conducting many new researches related to understanding cancers' cellular behavior, identifying novel therapeutic targets, and designing novel treatment strategies.

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Declarations

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