Role of the Immune Tolerance-Inducing Molecule Indoleamine 2,3-Dioxygenase in Gynecologic Cancers

Kazuhiko Ino*, Yuko Tanizaki, Aya Kobayashi, Saori Toujima, Yasushi Mabuchi and Sawako Minami

Department of Obstetrics and Gynecology, Wakayama Medical University, Wakayama, Japan

Abstract

Immune escape and acquisition of tolerance by tumor cells are essential to cancer growth and progression. Therefore, considerable attention has been paid to overcoming the immune resistance of tumors as a novel strategy for cancer therapy. This review focuses on the tryptophan-catalyzing and immunoregulatory enzyme indoleamine 2,3-dioxygenase (IDO), and its functional role in gynecologic cancers, such as endometrial cancer, ovarian cancer, cervical cancer, and vulvar cancer. IDO induces tolerance to the host immune surveillance through suppressing the proliferation of effector T-cells or natural killer cells and their killer functions within the tumor microenvironment. In gynecologic cancers, IDO is highly expressed in more than half of cases, and tumoral IDO expression is correlated with advanced surgical stage and impaired patient survival. In preclinical studies in mice, an IDO inhibitor 1-methyltryptophan suppresses tumor growth and peritoneal dissemination, and increases the efficacy of chemotherapeutic agents. In summary, IDO is a novel prognostic indicator for endometrial, ovarian, cervical, and vulvar cancers. IDO inhibition may be a promising strategy to restore host anti-tumor immunity and to enhance the anti-tumor potential of current chemotherapy, radiotherapy, and immunotherapy for gynecologic cancers.

Keywords: Endometrial cancer; Ovarian cancer; Cervical cancer; Vulvar cancer; Immune tolerance; Indoleamine 2,3-dioxygenase; Immunotherapy; Survival

Abbreviations: IDO: Indoleamine 2,3-dioxygenase; 1-MT: 1-methyltryptophan; TIL: Tumor-Infiltrating Lymphocyte; Treg: Regulatory T cell; NK cell: Natural Killer cell

Introduction

Gynecologic cancer mainly consists of three major tumors; endometrial carcinoma, ovarian carcinoma, and uterine cervical carcinoma, and also includes vulvar carcinoma. Most patients with International Federation of Gynecology and Obstetrics (FIGO) stage I-II early-stage gynecologic cancer achieve a favorable clinical outcome with surgery alone or with surgery plus postoperative adjuvant chemotherapy and/or radiotherapy. However, patients with FIGO stage III-IV advanced disease or recurrence remain to show the poor long-term survival. Therefore, in addition to conventional surgery, chemotherapy and radiotherapy, novel therapeutic strategies, such as immunotherapy and molecular-targeted therapy, are needed to further improve the survival of patients with advanced disease.

Immunotherapy has demonstrated promising results in basic and preclinical animal studies [1], and there have been several clinical trials in gynecologic cancer using immunologic modalities [2,3]. However, clinical applications have shown only limited efficacy [4], and this may be mainly attributed to tumor-induced immunosuppression. Therefore, much attention has been paid for understanding and overcoming the immune resistance mechanisms [5-9]. Recent studies have shown that indoleamine 2,3-dioxygenase (IDO) is one of the molecules involved in this tumor-induced immunosuppression [10-12]. In this review, we focus on the immunoregulatory enzyme IDO, and overview the recent studies

Role of IDO in Tumor-induced Immune Tolerance

Tumors are known to successfully escape the host immune surveillance, and this acquisition of immune tolerance is essential to cancer growth and progression. In various human cancers, multiple tumor-inducing immunosuppressive mechanisms have been demonstrated [5-9,13-15]; the down-regulation of Human Leukocyte Antigen (HLA) class I, loss of tumor antigens, lack of co-stimulatory signals, production of immunosuppressive cytokines and prostaglandin E2, induction of immunosuppressive host immune cells including regulatory T cells (Treg), Myeloid-Derived Suppressor Cells (MDSC), and tumor-associated macrophage, and expression of immunosuppressive molecules such as Fas ligand and programmed cell death 1 ligand 1 (PD-L1). In addition, recent studies have suggested that IDO is involved in tumoral immune tolerance [12].

IDO is an intracellular enzyme that catalyzes tryptophan at the initial and rate-limiting step [16]. Evidence for an immunosuppressive function of IDO was first documented in the mouse placenta, where IDO prevents rejection of the allogeneic fetus during pregnancy [17]. Subsequent studies have clarified the mechanisms of IDO immunosuppression in tumors. First, IDO expressed by tumor cells depletes tryptophan locally and produces a toxic tryptophan catabolite kynurenine, which causes growth arrest and the apoptosis of effector T-cells or natural killer (NK) cells that are extremely sensitive to tryptophan shortage, and also suppresses their killer functions [12,18-20]. Secondly, IDO expressed by antigen-presenting Dendritic Cells (DCs) within tumor-draining lymph nodes induces tolerance to tumor-derived antigens [21]. Lastly, IDO expressed by plasmacytoid DCs plays a critical role in conversion of CD4+CD25 T cells into

*Corresponding author: Kazuhiko Ino, MD, PhD, Professor and Chairman, Department of Obstetrics and Gynecology, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-0012, Japan, Tel: 81-(0)73-441-0631; Fax: 81-(0)73-445-1161; E-mail: kazuino@wakayama-med.ac.jp

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CD4⁺CD25⁺Foxp3⁺ regulatory T (Treg) cells, directly activating mature Tregs [22,23]. These findings suggest that IDO, in cooperation with Treg (and possibly MDSC and immunosuppressive cytokines), induces the immune tolerogenic microenvironment, which leads to tumor progression (Figure 1).

**IDO Expression and Function in Gynecologic Cancers**

In human cancer, Uyttenhove et al. [12] first demonstrated that IDO was expressed in various human cancer tissues. Subsequent studies have shown that IDO expression is correlated with disease progression or poor clinical outcomes in various histologic cancer types [24]. In gynecologic cancers including endometrial, ovarian, cervical, and vulvar carcinomas, associations of IDO expression with tumor progression or clinical outcomes have been extensively studied by the authors and others. The results of their studies are summarized in Table 1.

**Endometrial cancer**

In endometrial cancer, immunohistochemical analysis by Ino et al. [25] demonstrated that high IDO expression in tumor cells was found in 37 (46.3%) of the 80 cases, and was positively correlated with surgical stage, myometrial invasion, lymph-vascular space involvement and lymph node metastasis. Patients with high IDO expression had significantly impaired overall survival (OS) and Progression-Free Survival (PFS) compared to patients with no or weak expression of IDO. In their report, IDO expression was an independent prognostic factor for impaired PFS on multivariate analysis. These results indicate that IDO is a novel and reliable prognostic indicator for endometrial cancer.

Recent reports have shown the impact of tumor-infiltrating lymphocytes (TIL) on disease progression and clinical outcome, and suggested that TIL could be a surrogate marker for the immunological status within the tumor microenvironments [26,27]. In endometrial cancer, Ino et al. [28] showed that IDO expression is correlated with reduced numbers of CD8⁺ TILs and CD57⁺ NK cells, and high IDO expression with reduced TIL count is an independent prognostic factor for impaired survival. These findings suggest that IDO expression is associated with poor clinical outcome via suppression of TIL and/or NK cells within the tumor microenvironment.

**Ovarian cancer**

In ovarian cancer, Okamoto et al. [30] first reported that IDO was over expressed in paclitaxel-resistant ovarian cancer tissues in a gene expression profiling study using microarrays, and that patients with diffuse IDO expression have poor clinical outcomes in stage III-IV serous-type ovarian cancer. Similarly, another report demonstrated a relationship between IDO expression and impaired OS for advanced serous ovarian carcinoma, but not for other histological types [31]. Recent immunohistochemical study by Inaba et al. [32] using 60 ovarian cancer samples demonstrated that high IDO expression was found in over 70% cases with stage II-IV advanced diseases, and was significantly correlated with a low number of CD8⁺ TIL and impaired OS/PFS. These findings suggest that IDO acts as a prognostic indicator for ovarian cancer.

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**Figure 1:** Possible mechanisms of IDO-induced immune tolerance within the tumor microenvironment. IDO expressed by antigen-presenting dendritic cells within tumor-draining lymph nodes induces tolerance to tumor-derived antigens, while IDO expressed by tumor cells within the tumor microenvironment blocks effectors of adaptive immunity (CD8⁺ T-cells) and innate immunity (NK cells), in cooperation with Treg, MDSC, and immunosuppressive cytokines. This immune tolerogenic microenvironment leads to tumor growth and progression.

IDO: Indoleamine 2,3-dioxygenase; LN: Lymph node; DC: Dendritic cell; NK: Natural killer cell; TIL: Tumor-infiltrating lymphocyte; Treg: Regulatory T cell; MDSC: Myeloid-derived suppressor cell; IL-10: Interleukine-10; IL-6: Interleukine-6; TGF-β: Transforming growth factor-β; VEGF: Vascular endothelial growth factor.
To clarify the functional role of IDO in ovarian cancer progression, Inaba et al. [32] examined the behavior of IDO-overexpressing human ovarian cancer cells in vivo using a tumor-xenografted nude mouse model. In their report, increased peritoneal tumor dissemination was shown in IDO-overexpressing tumor intraperitoneally-transplanted mice. This effect was abrogated by administration of the IDO inhibitor 1-MT. These findings are consistent with another study showing a rapid tumor growth with reduced NK cell accumulation in IDO-expressing human ovarian cancer-transplanted nude mice [33]. Similarly, the IDO-induced tumor progressive effects were inhibited by 1-MT or IDO downregulation by short hairpin RNA targeting IDO [33,34]. Furthermore, a recent report by Qian et al. [35] has shown that IDO-positive human ovarian cancer cells suppress T-cell proliferation in vitro. Taken together, it is suggested that IDO enhances the ovarian cancer progression through induction of an immune tolerogenic tumor microenvironment against host effector T cell or NK cell attack [36].

Cervical cancer

IDO expression in cervical cancer and its association with clinicopathological factors and survival were immunohistochemically analyzed by Inaba et al. [37] in 112 stage IB-IIIB patients treated with radical hysterectomy. In their study, IDO was diffusely expressed in tumor cells in 29 (26%) cases and focally expressed at the invasive front in 29 (26%) cases, and the IDO expression was positively correlated with clinical stage and lymph node metastasis. Patients with diffuse IDO expression had significantly reduced OS and Disease-Free Survival (DFS). These findings suggest that IDO may be a post-operative prognostic indicator for cervical cancer. In addition, Nakamura et al. [38] reported that IDO was focally expressed in cervical intraepithelial neoplasia (CIN) 2 to 3 and that its expression was increased in microinvasive cancer, but absent in the normal cervical epithelium and CIN 1, suggesting the involvement of IDO in the progression of cervical neoplasia to invasive cervical cancer.
**Vulvar cancer**

IDO expression in vulvar Squamous Cell Carcinoma (SCC) has recently been reported [39,40]. Szurkowski et al. [39] evaluated the immunohistochemical expression of IDO and its impact on the recruitment of Foxp3+ Tregs within tumor nests in 76 patients with vulvar SCC. In their report, high IDO expression was associated with worse overall survival, and IDO expression was an independent prognostic factor for vulvar cancer, while the degree of intratumoral Treg infiltrates was not correlated with IDO expression or survival. In contrast, another immunohistochemical study in 286 vulvar cancer patients showed that IDO expression was present in 50.4% of the cases, although its expression was not associated with the number of intratumoral CD8+ TILs and Foxp3+ Tregs, or patient survival [40].

**Clinical Perspective of IDO-targeted Therapy**

To increase the efficacy of chemotherapy, radiotherapy, and immunotherapy, and further improve patient survival, overcoming the tumor-induced immune tolerance is needed. Therefore, IDO-targeted therapy to restore host anti-tumor immunity may have clinical potential [41,42]. Many data obtained from preclinical models demonstrate that IDO inhibition by 1-MT can significantly enhance the anti-tumor activity of various chemotherapeutic agents not only in murine tumors [43,44], but also in human gynecologic cancers [29,32]. Preclinical studies in mice have used 1-methyl-D-tryptophan (D-1-MT), because the D-stereoisomer of 1-MT was shown to be more effective in reversing T-cell suppression and more efficacious as an anticanter agent when compared to the L-isomer (L-1-MT) in tumor-bearing mice [44]. Thus, D-1-MT was initially selected for clinical trials and is currently being used in a phase I study in patients with relapsed or refractory solid tumors to determine the safety and efficacy of its administration at doses from 200 to 2000 mg daily [45,46].

In contrast, recent reports have demonstrated the superiority of L-1-MT. L-1-MT, but not D-1-MT, restored the T-cell proliferation arrest induced by IDO-expressing ovarian cancer cells [35]. Consistently, only L-1-MT, but not D-1-MT, was able to block IDO activity in human dermic cells [47]. Recent studies have shown that a novel IDO isoform IDO2 is also expressed in human tumors and that IDO1 is the preferential target of L-1-MT, while D-1-MT preferentially inhibits IDO2 [47-50]. In addition, one report showed that D-1-MT upregulates IDO1 expression in some human cancer cells and could have off-target effects, which should be carefully considered in further clinical trials with D-1-MT [51]. Besides 1-MT, a newly discovered potent IDO inhibitor hydroxamidine has recently been reported to have anti-tumor effects with strong IDO1-inhibiting activity *in vitro* and in preclinical animal models [52,53]. Further studies are necessary to select the optimal IDO inhibitors in future clinical trials for gynecologic cancers.

**Conclusion**

IDO induces immune tolerance within the tumor microenvironment. Tumoral IDO expression is found in more than half of gynecologic cancer patients with advanced staged disease, and is closely correlated with impaired patient survival. Furthermore, IDO overexpression enhances tumor progression and IDO inhibition by 1-MT in combination with chemotherapeutic agents results in potentiated anti-tumor efficacy and prolonged survival in preclinical studies. These findings lead to future clinical trials of IDO-targeted therapies for gynecologic cancers to enhance the antitumor efficacy of current chemotherapy, radiotherapy and immunotherapy.

**Conflict of Interest Statement**

The authors declare that there are no conflicts of interest.

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