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Gene Section
Review

IDO1 (indoleamine 2,3-dioxygenase 1)

Mee Young Chang, Alexander J Muller, George C Prendergast

Lankenau Institute for Medical Research, 100 Lancaster Avenue, Wynnewood PA 19096, USA (MYC, AJM, GCP)

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Identity

Other names: CD107B; EC 1.13.11.52; IDO; INDO

HGNC (Hugo): IDO1

Location: 8p11.22

DNA/RNA

Description

The human IDO1 gene is encoded on 10 exons which span 14,163 bps at chromosome 8p12-p11 (nucleotides 39,890,485-39,905,107). The murine IDO1 gene is similarly sized and localized to a syntenic locus on mouse chromosome 8A2.

Transcription

Transcription of the human IDO1 gene produces a full-length mRNA transcript of 1,572 nt. The promoter includes transcription factor sites that confer responsiveness to type I and type II interferons (IFN-alpha / IFN-beta and IFN-gamma respectively), most potently to IFN-gamma. Many cell types strongly increase IDO transcription after exposure to IFN-gamma, including myeloid cells (monocyte/macrophages and dentritic cells), fibroblasts, endothelial cells, epithelial cells and many tumor cell lines. STAT and IRF transcription factors function cooperatively to mediate induction of IDO1 expression by IFN-gamma, and mice lacking either IFN-gamma or IRF1 function are deficient in IDO1 expression during infections.

Pseudogene

None known.

Protein

Description

The IDO1 gene encodes a full-length protein of 403 amino acids with a predicted molecular weight of 45,332 Daltons. The open reading frame is preceded by a long, untranslated sequence. There is no Kozak consensus sequence present at the ATG start site in the open reading frame.

Expression

IDO1 is widely expressed in the body. High expression is seen in placental trophoblast giant cells of fetal origin, epididymis, gut (distal ileum and colon), lymph nodes, spleen, thymus and lung. IDO activity in many of these locations is markedly increased in vivo by LPS treatment. With the exception of epididymis, a common feature of sites of expression is extensive mucosal surfaces and/or large lymphoid compartments with immunoregula-tory roles. IDO1 is overexpressed in many human diseases including cancer, chronic infectious disease, allergy, autoimmune disease and other disorders characterized by local immune suppres-sion.

Localisation

IDO1 is a cytosolic enzyme with no known secreted or extracellular form.

Function

IDO1 is a single-chain oxidoreductase catalyzing the first, rate-limiting step of tryptophan degrada-tion in biosynthesis of the central metabolic regulator nicotinamide adenine dinucleotide (NAD) along the kynurenine pathway. In mammals, IDO1 does not

catabolyze excess dietary tryptophan, which is carried out by the liver enzyme TDO2, and NAD levels are not maintained by synthesis but by salvage from the diet. Thus, the role of IDO1 in mammals was obscure until it was discovered to be strongly induced by IFN-gamma and linked to immune control. The function of IDO1 in immune control is based on broad evidence that tryptophan depletion and/or kynurenine production suppresses T cell-mediated immunity. In particular, IDO1-mediated tryptophan catabolism in antigen-presenting dendritic cells appears to be an important mechanism to generate immune tolerance to cross-presented neoantigens, such as those that arise during allogeneic pregnancy or cancer.

Antiproliferation: Tryptophan catabolism by IDO1 has been suggested to mediate antiprolife-rative effects during infection, including directly on infectious microorganisms that may rely on trypto-phan for growth. With regard to the function of IDO1 in immune regulation, tryptophan depletion in the vicinity of an antigen presentation event has been suggested to limit T cell activation by preventing the cell division required by T cells to become activated upon appropriate presentation of antigen. Dendritic cells arising from monocytes acquire the ability to act as regulatory cells that suppress T cell proliferation through tryptophan catabolism by IDO1. The 1-methyl analogue of tryptophan (1MT) has been used widely to block IDO activity. When T cells are deprived of tryptophan, they arrest at a mid-G1 phase of the cell cycle. Restoring tryptophan does not restore the activation process, which requires a second round of T cell receptor signaling along with tryptophan. Together this information has suggested that antigen-presenting cells can employ IDO1 to restrict T cell activation by blocking T cell proliferation, due to tryptophan catabolism.

Apoptosis: The products of tryptophan catabolism by IDO1 include kynurenine and downstream products of the so-called kynurenine pathway that can induce apoptosis of thymocytes and Th1 but not Th2 helper T cells. Apoptosis induced by these products does not require Fas/Fas ligand interactions but are associated with activation of caspase-8 and the release of cytochrome c from mitochondria. When administered in vivo, some kynurenines can deplete specific thymocyte subsets like dexamethasone. Thus, the selective deletion of T lymphocytes by kynurenine production has been suggested as one mechanism through which tryptophan catabolism could blunt immunity under pathologic conditions.

Immune tolerance: Many studies illustrate how IDO1 overexpression can blunt immune responses to neoantigens. Cell lines overexpressing IDO1 limit antigen-specific T cell responses in vitro. In murine tumor cell lines, IDO1 overexpression renders tumor allografts resistant to immune rejection in vivo. Adenoviral-mediated IDO1 gene transfer into pancreatic islet cells is reported to prolong survival in allogeneic hosts. Similarly, ectopic expression of IDO1 is found to protect allogeneic lung transplants from rejection. CTLA-4 signaling induces IDO and pre-treatment of mice with CTLA-4-Ig to induce IDO expression suppresses rejection of pancreatic islet allografts. In a model of graft-versus-host disease, IDO1 overexpression completely blocks clonal expansion of alloreactive T-cell receptor (TCR)-transgenic T cells. Studies in other tissue allograft models confirm that IDO is a potent regulator of adaptive immune response. A consistent picture is provided by studies employing the pharmacological agent 1MT as an IDO inhibitor. 1MT exacerbates symptoms of experimental autoimmune encephalo-myelitis and abrogates the tolerogenic effects of CTLA4-Ig treatment in an islet-cell transplant model. Similarly, 1MT increases disease severity and mortality in a T cell-dependent colitis model, suggesting the role of IDO in the downregulation of Th1 responses within the gastrointestinal tract. Lastly, as discussed in more detail below, 1MT corrects immune escape mediated by IDO in a variety of allograft and transgenic (autochthonous) mouse models of cancer.

Maintenance of Pregnancy: IDO1 has been suggested to mediate immune tolerance during pregnancy on the basis of the ability of IDO inhibitor 1MT to act as an abortifacient in allogeneic but not syngeneic mice. IDO1 gene knockout studies do not replicate this effect suggesting a compensatory genetic effect or an IDO1-dependent effect of 1MT. Indeed, 1MT is no longer active in IDO1 knockout mice, demonstrating that 1MT must target IDO1 mediate its effects.

Null phenotype in mouse: IDO1-deficient mice are viable and fertile. in vitro generation of antigen-presenting dendritic cells (DCs) from IDO1-deficient bone marrow precursors appeared to be affected in the presence of GM-CSF, however, changing growth factor and adherence conditions abolished the observed differences (Flt3L and low-adherence dishes). Moreover, IDO1-deficient mice display a normal DC compartment in vivo and do not develop lethal autoimmune or lymphoproli-ferative disorders. Consistent with this observation, mice treated systemically for up to 28 days with 1MT or other IDO inhibitors do not appear to develop spontaneous autoimmunity. Together these observations imply that IDO1 is non-essential for self tolerance. In contrast, skin carcinogenesis studies reveal that IDO1-deficient mice are resistant to cancer initiation and carcinoma progression, due to an apparent inability to develop tumor tolerance.

Homology

Human IDO1 has 62% identity (77% similarity) with mouse IDO1 and 44% identity (64% similarity) with mouse IDO2. Human IDO1 has 44% identity (63% similarity) with human IDO2 and mouse IDO1 has 44% identity (64% similarity) with mouse IDO2.

Implicated in

Cancer

Note

IDO1 is observed to be highly expressed in many human cancers at the level of the tumor and/or the tumor-draining lymph node. Elevated tryptophan catabolism in the urine and blood of tumor-bearing patients has been recognized for many decades, perhaps explained by the discovery of common IDO1 overexpression in tumors.

Leukemia

Note

Patients with acute myeloid leukemia (AML) exhibit an increased ratio of Kyn/Trp in the serum and patients with higher Kyn/Trp ratios display a dramatically reduced survival. In adult T-cell leukemia/lymphoma (ATLL) that is caused by HTLV-1 infection, the serum kynurenine concentrations, Kyn/Trp ratio, and level of IDO mRNA expression are all significantly increased relative to healthy subjects. Interestingly, after chemotherapy, serum kynurenine concentrations are significantly reduced and tryptophan concentrations are significantly increased.

Breast cancer

Note

IDO1 expression has been reported in all breast cancer and non-cancer specimens as determined by semiquantitative RT-PCR, with higher levels observed in cancer specimens compared to non-cancer specimens. In this malignancy IDO1 has not been found to correlate to histologic classification, tumor size, lymph nodes metastasis, and survival rate after surgery. However, its expression has been reported to correlate to clinical stage and the serum level of immunosuppressive acidic protein (IAP) in breast cancer patient. In MMTV-Neu transgenic mice, an established mouse model of breast cancer, the IDO1 inhibitor 1MT slows tumor growth but does not arrest it. In contrast, 1MT cooperates strongly with paclitaxel, cisplatin, cyclophospha-mide, or doxyrubicin (all widely used in breast cancer treatment) to trigger regression of established tumors that are otherwise refractory to single-agent therapy.

Lung cancer

Note

IDO1 expression has been reported to be higher in cases of lung cancer and autologous non-malignant lung tissues than in lung cancer cell lines by quantitative real-time RT-PCR. No significant correlations between IDO1 expression and clinico-pathological parameters have been observed. In human non-small-cell lung cancer (NSCLC), immunohistochemical analysis suggests that IDO1 is expressed not by tumor cells but by eosinophilic granulocytes. IDO1 protein in NSCLC is enzy-matically active, implying that IDO-positive eosinophils may be competent to exert local immunosuppression. A significant relationship is found between the amount of IDO1-positive infiltrate and overall survival by follow-up analysis of lung cancer patients.

Skin cancer

Note

In the classical two-stage mouse model of skin carcinogenesis, phorbol myristate acetate (PMA) induces plasmacytoid dendritic cells (pDCs) in local draining lymph nodes to express IDO1, which confers suppressor activity to the pDCs. Significan-tly, IDO1-deficient mice display a tumor-resistant phenotype in this model of carcinogenesis.

Colon cancer

Note

IDO1 expression in human colon carcinoma cell lines dependent on IFN-gamma induction. Immuno-histochemical analysis of colon tumors indicated that IDO1 overexpression is associated with a significant reduction of CD3+ infiltrating T cells and higher occurrence of liver metastases in colo-rectal cancer patients. Conversely, no correlation was seen with tumor stage, tumor size, histologic grade, nodal status, gender, or age.

Pancreatic ductal adenocarcinoma (PDA)

Note

IDO1 is upregulated in metastatic PDA cells and associated with an increased number of FoxP3+ T regulatory cells (Tregs) in tumors. No correlation of IDO1 expression is observed with tumor histologic grade in PDA. In contrast, while non-metastatic PDAs are negative or only focally positive for IDO1, higher and broader expression of IDO1 is seen in both primary and metastatic tumors in patients with lymph node metastases (with stronger staining in metastatic foci).

Liver cancer

Note

In human hepatocarcinomas, immunohistochemical analysis revealed that IDO1 was strongly expressed in 36% of cases and weakly expressed in 64% of cases examined. In this study, IDO1 overexpression was significantly correlated with high rates of metastasis and poor prognosis.

Ovarian cancer

Note

IDO1 was found to be overexpressed in serous-type ovarian cancer where it was associated with decreased patient survival. IDO1 overexpression was also associated with resistance to paclitaxel.

Renal cell carcinoma

Note

Elevated levels of IDO1 mRNA were detected in >75% of clear cell type renal carcinoma, compared to normal kidney. In this study, IDO1 expression was associated with vascular cells in tumors and it correlated with improved long-term survival.

Cervical cancer

Note

IDO1 is expressed in cervical intraepithelial neo-plasia (CIN) and invasive cervical cancer. Immuno-histochemical analysis suggests IDO1 expression in antigen-presenting cells in both primary and invasive lesions. FoxP3+CD4+CD25+ Tregs appear in CIN and are increased in invasive cancer. No significant differences were observed in the proportion of Tregs in the stroma or epithelium (or between metastatic and non-metastatic cancers), but there was a significant increase in Tregs associated with IDO1 overexrpression in metastatic lymph nodes as compared to non-metastatic lymph modes.

Endometrial cancer

Note

High expression of IDO1 correlated with a reduced number of tumor-infiltrating lymphocytes (TILs) and natural killer (NK) cells in endometrial cancer. IDO1 overexpression was also positively correlated with myometrial invasion, nodal metastasis, and lymph-vascular space involvement, all of which contribute to disease progression and lower progression-free survival.

Uveal melanoma

Note

Primary uveal melanoma from tumor-bearing eyes and metastatic uveal melanoma from liver were not found to express IDO1 in situ. Also, IDO1 was not expressed in either primary or metastatic uveal melanoma cell lines unless they were stimulated by IFN-gamma. Addition of 1MT to IFN-gamma-treated uveal melanoma cell lines significantly diminished kynurenine levels. Together these findings suggested that in settings of IFN-gamma expression IDO1 upregulation may promote escape from T cell-mediated immune surveilance in uveal melanoma.

Inflammatory bowel disease (IBD)

Note

IDO1 mRNA is markedly induced in lesional colonic biopsies of IBD patients, being primarily expressed in CD123(+) mononuclear cells that infiltrate the submucosal areas of inflamed lesions. In Crohn's disease (CD), IDO1 is also strongly expressed in perifollicular regions of lymphoid follicles, with increased kynurenine and Kyn/Trp ratioes in colonic explant cultures (CECs) from CD patients. Immunohistochemical analysis of colonic biopsies taken from CD patients prior and after treatment with the TNF-blocking antibody infliximab caused a reduction in IDO1 expression in patients with good clinical response to infliximab, consistent with a potential benefit to IDO1 reduction in this disease.

Primary biliary cirrhosis (PBL)

Note

PBL is a chronic autoimmune cholestatic liver disease characterized by inflammatory destruction of the small bile ducts within the liver that eventually leads to cirrhosis. One study found a defective Treg compartment and an impaired IDO1 induction by IFN-gamma in peripheral monocytes isolated from patients with PBL.

HIV infection

Note

Infection of HIV or Simian immunodeficiency virus (SIV) increases IDO1 expression and functional IDO enzymatic activity both in vitro and in vivo. It is reported that patients infected with HIV have chronically reduced levels of plasma tryptophan and increased levels of kynurenine, suggesting the possibility of IDO1 activation. IDO1-expressing cells may protect HIV from clearance by allowing virally infected cells to become resistant to attack by T cell, or indirectly by promoting induction of acquired, antigen-specific tolerance to HIV antigens.

Depression

Note

Evidence exists of a link between IDO activity and mood. In serotonergic nerve terminals tryptophan is hydroxylated before conversion to serotonin (5HT). Lower levels of serotonin in the brain are associated with depressed mood. Tryptophan availability limits de novo synthesis of serotonin and tryptophan depletion has been associated with depressive symptoms in patients with remitted major depressive disorder, resulting in a distur-bance of mood in subjects with a family history of affective illness.

Given the proposed role of IDO in maintaining pregnancy, the linkage between IDO activity and mood may be relevant to postpartum depression. Typically this phenomenon occurs within a few days after delivery until the tenth day postpartum. An association has been noted between Kyn/Trp ratio and the severity of depressive symptoms in the early puerperium, suggesting that an increased degradation of typtophan relates to the occurrence of postpartum blues. Conversely, a decrease in Kyn/Trp ratioes has been reported in women with stable mood after delivery.

Some evidence exists that inflammatory changes in the brain that may be associated with IDO1 expression are pathological features of both depression and dementia. Pathological changes have been associated with a reduction in the neuroprotective components of the kynurenine pathway (e.g. kynurenic acid) and an

increase in the neurodegenerative components (e.g. 3-hydroxy-kynurenine acid and quinolinic acid). These changes are postulated to cause neuronal damage and predispose chronically depressed patients to dementia. In Alzheimer's patients, plasma Kyn/Trp ratioes have been observed to correlate with the degree of cognitive deficit. Also, immunohisto-chemical analysis suggests that IDO1 is abundant in the brains of Alzheimer's patients compared to controls. Similarly, relative elevations in Kyn/Trp ratio have been found in plasma from patients with Huntington's or Parkinson's disease compared to controls. Notably, depressive symptoms affect up to 50% of Alzheimer's patients, 41% of Huntington's patients, and 40% of Parkinson's patients.
Further support for a link between IDO1 elevation and depressed mood are found in patients with autoimmune diseases, where symptoms have been associated with increased tryptophan catabolism. Enhanced tryptophan degradation was found in systemic lupus erythromatosus, rheumatoid arthritis, sarcoidosis, and a mouse model of multiple sclerosis. It has also been noted that a higher proportion of patients infected with Hepatitis C virus (HCV) have lower serum tryptophan concentrations and depression relative to healthy volunteers.

Defense against mycoplasm infection

Note

IDO1 has been implicated in host defence against certain pathogens such as Chlamydia pneumoniae, Toxoplasma gondii, group B streptococci, and mycobacteria through its ability to deplete trypto-phan and thereby inhibit pathogen replication. IDO1 has also been observed to inhibit the replication of cytomegalovirus and herpes simplex virus in vitro.

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