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REVIEW

The modulation of enzyme indoleamine 2,3-dioxygenase from dendritic cells for the treatment of type 1 diabetes mellitus

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Abstract: Diabetes mellitus type 1 (DM1) is an autoimmune disease in which β-cells of the pancreas islet are destroyed by T lymphocytes. Specific T cells are activated by antigen-presenting cells, mainly dendritic cells (DCs). It is already known that the regulation of tryptophan pathway in DC can be a mechanism of immunomodulation. The enzyme indoleamine 2,3-dioxygenase (IDO) is present in many cells, including DC, and participates in the metabolism of the amino acid tryptophan. Recent studies suggest the involvement of IDO in the modulation of immune response, which became more evident after the in vitro demonstration of IDO production by DC and of the ability of these cells to inhibit lymphocyte function through the control of tryptophan metabolism. Current studies on immunotherapies describe the use of DC and IDO to control the progression of the immune response that triggers DM1. The initial results obtained are promising and indicate the possibility of developing therapies for the treatment or prevention of the DM1. Clinical trials using these cells in DM1 patients represent an interesting alternative treatment. However, clinical trials are still in the initial phase and a robust group of assays is necessary.

Keywords: autoimmunity, immunoregulation, diabetes mellitus type 1, clinical trials, dendritic cells, indoleamine, tryptophan, tolerance

Introduction

Diabetes mellitus type 1 (DM1) is an autoimmune disease with massive destruction of pancreatic β-cells, with lymphocyte and macrophage infiltrates in the islets of Langerhans.[1,2] Although already approved therapies to DM1 are available, they are still poorly effective in controlling the progression of diabetes. Recent advances in the studies of DM intended to develop cellular therapies, such as the regeneration of pancreatic β-cells from transplantation of precursor stem cells.[3,4] To reverse the immunopathogenesis of the DM1, some authors propose an early vaccination as prophylaxis. Also, restoration of immune tolerance to self-antigens in DM1 patients is considered a promising therapy.[5] In this sense, treatment with immunoregulatory cells specifically explores the modulatory capacity of indoleamine 2,3-dioxygenase (IDO).

It is known that the enzyme IDO, expressed in dendritic cells (DCs) and other cells, participates in the metabolism of tryptophan (TRP). Recent studies suggest the participation of IDO in the modulation of the immune response, which became more evident after the in vitro demonstration of IDO production by DC and of the ability of these cells to inhibit lymphocytes via the TRP pathway.[6–10] In this subject, experiments with macrophages and human DC expressing IDO have demonstrated that the presence of IDO blocks in vitro proliferation of T cells.[7] IDO1 is an immunomodulatory molecule

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with potential effects on various diseases including cancer and autoimmunity.[11,12] IDO2, as well as IDO1, is implicated in TRP catabolism and modulation of immune response. IDO2 seems to act in a distinct way from IDO1. However, the specific contributions of IDO2 to physiology are still unknown.[13]

A recent study suggests that IDO1 activity may correlate with the pathogenesis of diabetes mellitus type 2 (DM2) since it was significantly increased in these patients.[14] Reduction in IDO1 levels also seems to be related to the pathogenesis of DM1,[15] since in experimental diabetes, toll-like receptor (TLR) 3-deficient mice presented a more robust disease, accompanied by the absence of IDO1 induction in pancreatic lymph nodes.

However, new mechanisms to control DM1 as well as to elucidate the participation of the IDO1 enzyme in the DC response are under development. In this context, the study of the mechanism of action of IDO1 and its relationship with the immunological mechanism can be relevant for the future development of vaccines or drugs. Hence, the aim of the present review was to describe the participation of DC in the control of the immune response on DM1, as well as the regulation of the IDO1 enzyme in these cells.

Immunological mechanisms of type 1 diabetes mellitus

Current studies demonstrate that DC can participate in the regulation of DM1,[16] since it is a disorder related to the action of autoreactive T cells against pancreatic β-cells.[17] $CD11c^+$ $CD11b^+$ $CD8\alpha^-$ DC activates T lymphocytes that initiate the process of insulitis and eliminates pancreatic β-cells.[18,19] Autoantibodies subsequently participate in inflammatory process and can be used as markers of immune response.[20] It is also known that the enzyme IDO, present in DC, participates in the immunity by regulating the proliferation of T cells.[7]

Indoleamine 2,3-dioxygenase and the kynurenine pathway

IDO is one of the two enzymes that catalyze the limiting step of the degradation of TRP through the kynurenine (Kyn) pathway. Studies showed that the tryptophan 2,3-dioxygenase (TDO) and IDO enzymes catalyze the conversion of TRP to *N*-formyl kynurenine.[21,22] Unlike TDO, expressed only in the liver, IDO is found in various organs, tissues, and cell types, such as stromal, hematopoietic, tumor, lymphoid, and dendritic cells,[21,22] and expressed often in tissues with large mucosa, such as the gastrointestinal tract and lung.[23]

IDO is an oxygenase enzyme with a heme group[24] composed of two domains – major and minor[25] – encoded by two closely related genes (*IDO1* and *IDO2*), located on human chromosome 8.[26,27] In the TRP catabolism, IDO is responsible for the oxidative cleavage of double bond present in the indol fraction of TRP, resulting in the formation of *N*-formyl kynurenine.[25] The kynurenine pathway (Figure 1) is the main route of degradation of TRP, since 99% of this ingested amino acid is metabolized by this way. The kynurenines generated include kynurenic acid, 3-hydroxykynurenine, picolinic acid, quinolinic acid, and kynurenine itself.[25,28,29] IDO enzyme is able to inhibit the in vitro proliferation of T cells by the catabolism of TRP via kynurenines, participating in the modulation of immune response.[30]

Several studies indicate that the transcription process is well controlled after the activation of IDO, with activation of genes of inflammatory mediators, such as interferon (IFN)-α, IFN-β, and IFN-γ. Among several IDO inducers, lipopolysaccharide (LPS)-induced IDO expression was found in blood, muscle, brain, liver, and lung. LPS administration induces increased concentrations of TNF-α, IL-10, and Kyn, and a depletion of TRP indicating an elevated activity of IDO.[28,31]

Although IDO expression is rapidly induced by IFN-γ alone or associated with interleukin (IL)-1β, IDO secretion also occurs in DC after signaling by transforming growth factor beta 1 (TGF-β1), which demonstrates a mediation of its regulatory function.[7,30,32–34] The mechanism of control of IDO expression is not fully understood but post-translational modifications are relevant in this process. Also, the induction of IDO in DC can occur through immunomodulatory properties of molecules, that inhibit the pathways of T cells activation via T cell receptor (TCR), Cytotoxic

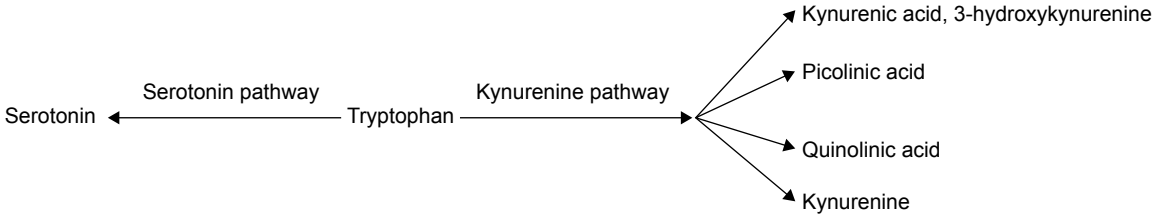

Figure 1 Kynurenine and serotonin pathway.
Note: Tryptophan participates in serotonin and kynurenine pathways. Data from.[25,28–30]

T-lymphocyte-Associated Associated Antigen 4 (CTLA-4), Toll like receptors (TLR) and CD40.[23,35]

The immunoregulatory properties of IDO on DC

The role of IDO on immunosuppression was first discussed in 1998 when Munn et al demonstrated that when pregnant rats were treated with an inhibitor of the IDO enzyme called 1-methyl tryptophan, maternal lymphocytes initiated a process of rejection to the fetus. Subsequently, the studies of IDO in immunosuppression extended to regulation of tumors, inflammatory, allergic and autoimmune diseases, the enzyme being recognized as a regulator of immunity.[34,36,37] This regulatory action of IDO is possibly due to the combination of the effects of TRP degradation and of the accumulation of the kynurenine metabolites that act on the hydrocarbon ring present at the TCR.[17,34]

IDO can affect the ability of DC to present antigens and stimulate T cells. Also, the catabolism of the TRP is a central pathway to this immunosuppressive response. In this sense, IDO can induce the depletion of TRP and the accumulation of kynurenine metabolites, as exemplified in Figure 2.[23,34] The T cells activated by DC expressing IDO are able to initiate the cell cycle. However, the enzymatic activity of IDO leads to a significant decrease of TRP, inducing the cell cycle arrest and enhancing T cell apoptosis. IDO1 was described as the first rate-limiting enzyme acting on the degradation of TRP since the enzyme activity results in the depletion of TRP and inhibition of T lymphocytes.[38] The initial step of the kynurenine pathway involves the oxidation of TRP. TRP derivatives have pleiotropic effects on homeostasis processes. IDO and TDO are heme-containing enzymes that catalyze the O_2-dependent oxidation of L-TRP in biological systems. Studies report that IDO and TDO react using the same mechanism. For IDO, a ferryl species accumulates in the steady state. However, there is no evidence for the accumulation of this compound during TDO catalysis. Serotonin and melatonin are two TRP-derived compounds produced in humans, among others.

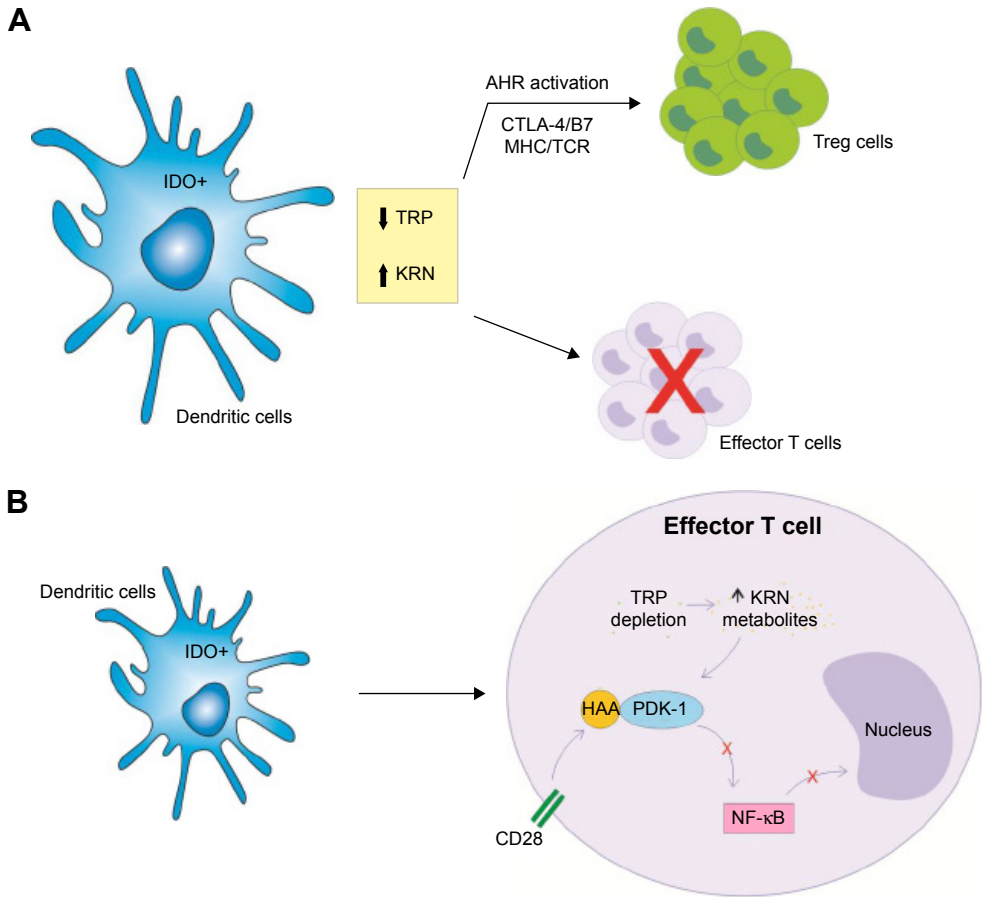

Figure 2 IDO and DC in the regulation of the T cell responses through the degradation of TRP and kynurenine metabolites.
Notes: (**A**) Depletion of TRP by IDO increases the metabolites of kynurenine and blocks T effector cell proliferation, favoring Treg differentiation. (**B**) Intracellular events in T effector cells in consequence of IDO activity in DCs.
Abbreviations: AHR, aryl hydrocarbon receptor; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DCs, dendritic cells; HAA, 3-hydroxyanthranilic acid; IDO, indoleamine 2,3-dioxygenase; KRN, kynurenine; MHC, major histocompatibility complex; NF-κB, nuclear factor kappa B; PDK-1, phosphoinositide-dependent kinase 1; TCR, T cell receptor; Treg, T regulatory; TRP, tryptophan.

Also, indole ring breakdown through the "kynurenine shunt" produces a number of molecules involved in inflammation, immune response, excitatory neurotransmission, and many other functions, such as L-kynurenine, kynurenic and quinolinic acids, or the coenzyme nicotinamide adenine dinucleotide (NAD^+).[39–42]

Recent research showed that catabolism of TRP mediated by IDO inhibits the immunoregulatory kinase mammalian target of rapamycin (mTOR), with the autophagy induction.[43] So, IDO was proposed to control inflammatory responses and immune tolerance coordinately by the pathways of TRP deficiency and sufficiency, via the integrated stress kinases namely general control non-depressible 2 (GCN2) and mTOR, respectively.[43,44] However, the role of GCN2 in immune response and suppression is not clearly established. Conflicting data showed that, in lupus-prone mice, activation of GCN2 reduced anti-DNA antibodies, implicating GCN2 signal in limiting autoimmunity.[45] However, a recent study described that kinase GCN2 is not related to the suppression of antitumor response by TRP catabolism.[46]

Tryptophan catabolites or starvation induce a regulatory environment affecting both $CD8^+$ and $CD4^+$ T cells. Recent studies showed that TRP catabolites result in GCN2 kinase-dependent downregulation of the TCR zeta-chain in $CD8^+$ T cells in mouse model. Also, TRP catabolism includes the emergence of a regulatory phenotype in naive $CD4^+$ $CD25^-$ T cells via TGF-β induction of the forkhead transcription factor Foxp3, capable of controlling diabetogenic T cells.[47,48]

The metabolites generated by the IDO activity are potent inhibitors of T cell activation. Some compounds such as 3-hydroxyanthranilic acid (3-HAA) are able to block T cells by interfering in the nuclear factor kappa B (NF-κB) pathway via inhibition of phosphoinositide-dependent kinase 1 (PDK-1), a mediator of NF-κB activation through CD28 signaling[49,50] (Figure 2). Besides that, kynurenine is also involved in the generation of T regulatory (Treg) in periphery, another important mechanism to control T cell responses. In lymph nodes, IDO controls conversion of $Foxp3^+$ Tregs to T helper (Th) 17 cells.[51] In this way, TRP metabolites are able to ligate to aryl hydrocarbon receptor (AHR), a cytoplasmic transcription factor, favoring differentiation of naive T cells to Tregs but not to Th17 cells.[52] However, literature suggests that other signaling pathways are also relevant, like the CTLA-4/B7 signaling and the major histocompatibility complex (MHC)–TCR interaction.[23,53]

Related to IDO therapeutic potential, synergistic treatment with TGF-β can result in a burst of regulatory kynurenines that contribute to establishing a state of "infectious tolerance". TGF-β activates the tolerogenic pathway of TRP catabolism – mediated by IDO.[54] IDO can be associated with the pathogenesis of persistent infections, and Treg cells might play an important role in the direct control of innate immune responses. According to an infectious tolerance model, Treg cells inhibit neutrophil function and promote their apoptosis by the induction of suppressor cell populations. LPS-activated Treg cells induce IL-10 and TGF-β1 secretion, inhibit IL-6 production, and also induce the expression of heme oxygenase-1 (HO-1) and the suppressor of cytokine signaling 3 molecule (SOCS3).[55,56]

Tregs induce IDO expression in DCs and tolerogenic DC induce conversion of naive T cells to Tregs. Both myeloid-derived suppressor cells (MDSCs) subset and tolerogenic DCs can control self-reactive immune responses by promoting the expansion of Treg population. MDSCs require direct contact with activated T cells, which leads to the production of IDO.[57]

A recent report showed that high-dose IL-4 inhibits the $CD103^+$ DC differentiation by inducing high levels of IDO. Interestingly, IL-4 diminished IDO expression in DCs in a dose-dependent manner. DCs generated under low concentrations of IL-4 favored Treg cells differentiation, which depend on IDO produced by $CD103^+$ DCs.[58]

Therapy with tolerogenic DC in diabetes mellitus

The conventional DM therapies basically include medications to control glucose and insulin levels. However, with the wide knowledge on cell biology, immunology, and biotechnology, cell therapy has been gaining prominence.[59] It can be used in the treatment of infections, autoimmune diseases, cancer, metabolic diseases, and tissue degeneration.[59,60] Also, cell therapy is becoming the alternative treatment of DM1 and several studies approach this theme in different ways.[61]

Studies demonstrate the possibility of development of in vitro insulin-producing cells with characteristics similar to pancreatic β-cells, using embryonic stem cells as source. Replacement of pancreatic β-cells has already been considered as an alternative to treat DM1.[62] Jalili et al prolonged islet allograft survival by preventing immune response. They induced a local immunosuppressive activity by stable IDO induction in bystander fibroblasts.[63] Also, administration of endovenous anti-CD3 monoclonal antibodies in patients newly diagnosed with DM1 results in the reduction of circulating lymphocytes as well as C-peptide, insulin, and glycated hemoglobin (HbAL1c) values.[64,65] In addition, experiments combining transplantation of autologous hematopoietic stem

cell and immunosuppression protocol based on endovenous cyclophosphamide and anticytoplasmic globulin restarted the immune system without autoreactive memory to the regenerated pancreatic β-cells. A high percentage of patients obtained insulin independence, without mortality or new toxic effects.[66–68]

Among therapies, DC therapies can be highlighted for autoimmune diseases such as DM1, since these cells participate in the pathogenesis of this disease.[69,70] DC therapies are evaluated for the treatment of infectious diseases, tumor, autoimmune diseases, transplants, and allergies.[50,69,70] In this context, it is known that plasmacytoid type DC (pDC), that participate in the immune response and the generation of tolerance, can act in the DM1 in the control of the regulatory and pathogenic T cells.[17,34]

In order to develop therapies for DM1 using tolerogenic DC, a study was performed ablating the myeloid DC (mDC) and pDC mediated by diphtheria toxin receptor in nonobese diabetic mice (NOD). The results showed that, with the ablation of mDC, prevention of the development of DM was achieved. However, with the ablation of pDC, an increase in the severity of the insulitis was observed, accompanied by the loss of natural killer T cells (NKT) and a decrease of IDO. Since IDO enzyme is an inhibitor of T cell response, the decrease of pDC or the inhibition of IDO by the use of 1-methyl-D-tryptophan (1-MT) increased the aggressiveness of the insulitis and the destruction of pancreatic β-cells. Also, the ablation of pDC caused reallocation of NKT cells that aggravates the insulitis, while the restoration of pDC normalized the insulin and NKT levels. The IFN-γ secretion by the NKT induced IDO production by DC, interconnecting these responses. Finally, it was concluded that pDC, IDO, and NKT can act together to prevent insulin production and, consequently, the development of DM1.[71,72]

Another study demonstrated that NOD mice have a deficiency in the signaling and functioning of the IDO enzyme, even after stimulation of pDC with TGF-β1. IDO could only be stimulated by this cytokine in the presence of a basal amount of this enzyme in the pDC. So, in order to initiate the phosphorylation cascade and the consequent protein signaling, it was necessary to perform a forced induction of the IDO in the pDC and the stimulation with TGF-β1. IDO signaling generated a positive feedback with TGF-β1, alternatively activating the NF-κB pathway.[17]

A recent study showed that a chimeric vaccine composed of the proinsulin and cholera toxin B subunit (CTB-INS) was able to suppress DM1 onset in NOD mice and upregulated enzyme IDO1 in human DC. This vaccine activated the tumor necrosis factor associated factor (TRAF) super-family receptor (TRAFR) pathway and led to the upregulation of IDO1 biosynthesis in CTB-INS inoculated DC. The control of NF-κB-inducing kinase (NIK) post-translational stability may be essential for the modulation of non-canonical NF-κB signaling pathway. Evidence suggests that TRAF2, TRAF3, and TRAF6 are critical to negative regulation of NIK activity. The CTB-INS vaccine acts in the TNF receptor-dependent signaling pathway of the noncanonical NF-κB signaling pathway resulting in the suppression of mediated DM1.[73]

DCs present autoantigens of pancreatic β-cells for self-reactive T lymphocytes. They are also involved in the deletion of autoreactive T cells. A report showed that targeting of DCs with beta cell antigens was able to achieve deletion of autoreactive cytotoxic T cells in NOD model.[74]

After treating DC with CTB-INS vaccine, an increase in the degradation of the TRP, a reduction in cell maturation functions, and an augment of the IDO1 synthesis were observed. This biosynthesis was reduced with NF-κB blockers reinforcing the role of this factor in the induction of IDO. All these findings, combined with the fact that this does not interfere with the monocytes differentiation into DC, open the possibility of developing safe and effective immunotherapeutic strategies for the prevention of autoimmunity that occurs in DM1.[16]

A clinical trial using DC for the treatment of DM1 is currently underway.[75–79] The vaccine consists of autologous monocyte-derived DC treated ex vivo with antisense phosphorothioate-modified oligonucleotides targeting the primary transcripts of the CD40, CD80, and CD86 co-stimulatory molecules, generating DC with immunoregulatory properties. The safety Phase I study[80] allowed to conclude that the use of tolerogenic DC in patients with DM1 was well accepted and safe, without adverse effects or toxicity.[76] In Phase II, the modulatory capability of DC collected via leukapheresis and engineered ex vivo via incubation with antisense DNA oligonucleotides targeting the primary transcripts of CD40, CD80, and CD86 will be evaluated.[80,81]

Final considerations

Nowadays, DC therapies to DM1 have focus on the immunoregulatory properties of these cells through their maturation and on the action of the IDO, an enzyme that participates in the metabolism of TRP and causes accumulation of the metabolites of kynurenines and consequent blockade of T lymphocyte proliferation. As shown here, the use of DCs in cell therapies in DM1, although recent, already presents

promising results since it has been proven that the IDO enzyme can be modulated in DC in a tolerogenic way. In this sense, it was possible to conclude that recent studies have demonstrated that DC expressing tolerogenic IDO may be effective in regulating the immune response of DM1. Therefore, the data support the suggestion of the application of tolerogenic DCs to induce tolerance in DM1. It is important to highlight that studies with DC on DM1 are in clinical phase and the results obtained heretofore are promising since they indicate the possibility of developing therapies for the treatment or prevention of the DM1. However, clinical trials are still in the initial phase and a more robust group of assays to confirm this proposition is necessary.

Disclosure

The authors report no conflicts of interest in this work.

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