Tolerogenic Dendritic Cell, an Unknown Cell in Celiac Disease

Farzaneh Kheiri¹, Mohammad Rostami-Nejad²*, Davar Amani¹ and Mohammad Javad Ehsani-Ardakani²

¹Department of Immunology, School of Medical Science, Shahid Beheshti University of Medical Sciences, Tehran, Iran
²Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Corresponding Author: Mohammad Rostami-Nejad, Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Received: November 14, 2019; Published: December 12, 2019

Abstract

Celiac disease is an immune-related disorder that occurs as a result of gluten intolerance and is associated with chronic small intestinal enteropathy and occurs in genetically susceptible patients. Dendritic cells are a bridge between innate and acquired immunity and can modulate immune responses in celiac disease by altering their phenotype. It has also been proven that different types of DC subtypes participate in the pathogenesis of celiac disease that among them tolerogenic dendritic cells (tolDCs) play a central role in inducing immune tolerance and can lead to differentiation of Tregs to maintain intestinal immune tolerance versus inflammatory responses in patients with celiac disease and other autoimmune disorders. This review illustrates the characteristics of tolerogenic dendritic cells and their role in celiac disease.

Keywords: Celiac Disease; Glutens; Tolerogenic Dendritic Cell, Immune Tolerance, Intestine

Introduction

Celiac disease (CD) is immune-dependent chronic small intestinal enteropathy with accumulation dendritic cell induced by gluten in genetically susceptible patients. The prevalence of celiac disease is universal and affected about 1% of the general population with nation differences [1]. Mucosal innate and adaptive immunities, environmental factors, genetic background, microbiota, gluten intake are the main cause of CD pathogenesis [2]. Gluten protein contains glutenins and prolamins and it finds in wheat, rye, and barley [3]. In patients with celiac disease, incomplete digestion of gluten peptides by the epithelial barrier via transcellular or paracellular direction gains entry to the lamina propria. After that these detrimental peptides start the activation of both immune responses (adaptive and innate immune) [4]. The best available treatment is a lifelong gluten free diet (GFD).

Dendritic cells (DCs) are one of immune cells that is an important player in CD. These cells are significant to determine the fate of immune responses (immunity or tolerance) and immune cells such as antigen-specific T cells and B cell activation interface dietary antigens like gluten. So, the imbalance in DCs function can disturb immune tolerance directly and cause autoimmune disease [5,6]. Moreover, DCs in gut homeostasis plays an important role in CD. Since they can process glutens in wheat and induce tolerance to self-antigens [7,8].

DCs have several subtypes that involved in CD such as tolerogenic DCs (tolDCs), plasmacytoid DCs (pDCs) [9,10]. Tolerogenic DCs (tolDCs) are central and peripheral tolerance actors in the body, they can oversee to homeostasis and inhibit inessential inflammation [11]. tolDCs have a reduced stimulatory capacity and high production of anti-inflammatory cytokines (i.e. IL-10). Their immunomodulatory properties proceed the differentiation of Foxp3+ Tregs that are known to suppress effector T cells and inhibit the synthesis of pro-inflammatory cytokines such as IFNγ, IL- 12 and TNF-α [12,13].

Citation: Mohammad Rostami-Nejad., et al. “Tolerogenic Dendritic Cell, an Unknown Cell in Celiac Disease”. EC Gastroenterology and Digestive System 7.1 (2020): 01-07.
Tolerogenic dendritic cells

In humans, dendritic cells originate from bone marrow precursors, which migrate through the blood to lymph nodes and non-lymphatic tissues, where they are ultimately differentiated and do their mission [14]. DCs recognize environmental signals like components of microorganisms, endogenous molecules via surface and intracellular pattern recognition receptors (PRRs) including Toll-like receptors (TLRs), NOD-like receptors (NLRs), and the RNA helicase RIG-I-like receptor (RIG); these receptors initiate signaling cascades [15]. DCs have the ability of immune response regulation. DCs present antigens to T cells in secondary lymphoid organs so they migrate from peripheral tissues [16].

DCs are classified by their developmental stage (immature or mature), functional properties (immunogenic or tolerogenic) and location. For example, CD8+ DC and CD11b+ DCs in spleen, CD103+CD11b- DCs and CD103+CD11b+ DCs in intestine and pDCs [17]. Moreover, there are DCs throughout the intestine the lamina propria (LP) of the small and large intestine, the isolated lymphoid follicles, the Peyer patches (PPs), and the mesenteric lymph nodes (MLNs) [5]. tolDCs are one of DCs independent cell lineage and heterogeneous group of DCs [17]. tolDCs have several unique properties that distinguish them from other DCs and they have functional plasticity depend on the local microenvironment and on inflammatory stimuli. tolDCs includes immature DCs (iDCs) and semi-mature DCs (semi-mDCs). Both immature (iDCs) and semi-mature DCs (semi-mDCs) can lead to tolerance [18].

Immature DCs via various PRRs can recognize environmental stimuli (pathogens, drugs, injury), intracellular antigens process in inflammatory tissues, then drive to mature DCs. Mature DCs migrate to secondary lymphoid tissues where they present the processed antigens to naïve T cells to drive effector T cells and after that lead to immunity against various infections. But in homeostatic-state immature DCs phagocytes and process antigens in healthy tissues and then present the processed antigens to naïve T cells to drive to anergic T cells and regulatory T cells for induction tolerance [19].

Mature DCs (mDCs) have high expression of MHC-II, co-stimulatory molecules and release pro-inflammatory cytokines in response to several stimuli such as pro-inflammatory cytokines and microbial components. Unlike immature DCs (iDCs) can antigen uptake more efficiently via several mechanisms, like macropinocytosis, receptor-mediated endocytosis, and phagocytosis. Moreover, iDCs characterized by low-level expression of MHC-II and co-stimulatory molecules, which their interaction with T cell, lead to anergy [20]. iDCs can uptake apoptotic products, lead to Treg cell expansion and in resulting presenting self-antigens to CD4+ T cells they cause peripheral tolerance [21]. The ability of iDCs is the induction of tolerance, but mDCs can induce immunity [22], therefore abnormal function these DCs subtypes is may be related to the initiation of autoimmune diseases [18].

Although there is no full definition and characterization of tolDCs. However, tolDCs are relatively resistant to activation/maturation-inducing signal and tolDCs as a player lead to tolerance by various actions, such as peripheral Treg cells development [19].

Tolerance mechanisms by tolDCs

Tolerance is a mechanism that inhibits immunity to an individual’s own antigens or non-self-antigens. In the intestine, tolerance induced for commensal microorganisms and dietary of food [23]. Under steady-state conditions, DCs have high tolerogenic properties and can polarization of T cells to Treg to keep the host from harmful inflammatory immune responses to various innocuous antigens. Also, DCs can distinguish between harmful, dietary antigens and commensal microbiota and after that they initiation immune response versus pathogens. If tolerogenic and proinflammatory responses failure to adjust by dendritic cells lead to chronic inflammatory conditions such as CD [24,25]. tolDCs manage central tolerance via clonal deletion, the suppression of memory T cell responses, T cell anergy, and the differentiation of regulatory T cells (Tregs). Also, tolDCs inhibit effector T cells and induce Tregs differentiation in the periphery tissues [26,27].

Intestinal DCs can drive to Tregs, express gut-homing properties to lymphocytes, so, they interact with other cells by many receptors. one of these receptors is co-stimulatory molecules CD80/CD86. tolDCs have lesser expression CD80/CD86 on the surface than other DCs, so these molecules after interaction with CD28 on T cells induce T cell activation [18,20].

tolDCs express high-level programmed cell death ligand-1 (PDL-1), PDL-2 and the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), these immune checkpoints are co-inhibitory molecules and suppress active T cells. Which competes with CD28 for binding to CD80/CD86.
Tolerogenic Dendritic Cell, an Unknown Cell in Celiac Disease

CD86 ligands. The interaction between CTLA-4 on Treg cells and CD80/CD86 on DCs leads to a tolerogenic profile in DCs and there is a mutual correlation. Therefore, tolDCs can suppress active T cells especially CD8+ T cell function, proliferation, development inducible Treg cells (iTreg cells) and limit inflammation [28-31]. Popat., et al. shown that CTLA-4 has related to CD and patients have a defect in this molecule and probably it has a regulatory role in this disease [32]. When T cells continue in an unresponsive state in resulting antigen encounter in the absence of costimulatory signals of DCs, anergy can happen. Anergy can induce via molecules CTLA-4 that they compete for binding with CD28, its ligands CD80/CD86 [27,33]. Anergy or functional inactivation induced by the interaction between PDL-1 and PDL-2 on tolDCs and PD-1 on T cells, as a result, tolDCs can keep tolerance and in the gut that suppress inflammatory disorders such as celiac disease [34-36]. According to Ponce de León PD-L expression increases in small bowel mucosa of individuals of CD by immunohistochemistry and all patients with a various grade of immunoreaction expressed PD-L1 [37].

tolDCs release anti-inflammatory cytokines such as IL-10, TGF-β and produce retinoic acid (RA) but can't high production pro-inflammatory cytokines. TGF-β leads to differentiation IL-10-producing Treg cells and IL-10 inhibits produce pro-inflammatory cytokines (IFN-γ, IL-12 and TNF-α). Therefore, these cells cause suppression of effector T cell function and expansion, and Treg differentiation and finally lead to immune tolerance [12,20].

Studies have shown that anti-inflammatory cytokines such as IL-10 are high in CD. Also, the levels of IL-10 are higher than untreated CD patients, moreover the ratio IL-10/ IFN γ in inflamed non-celiac, control, and treated CD mucosa is lesser [38]. This contradictory inflammatory and anti-inflammatory environment suggest that regulatory mechanisms are working to counter the abnormal gliadin-induced activation in untreated celiac disease [39]. Exogenous IL10 can suppress gliadin-specific Th1 and decreases expression of CD80/CD86 costimulatory molecules [38]. Torres., et al. have shown IL-10 release in the lamina propria patients with CD especially in areas with inflammatory cells has high immunoreactivity [40].

Indoleamine 2,3-dioxygenase (IDO) reported high expression in tolDCs, this enzyme can suppress T cell response, the development of Tregs, suppress and apoptosis effector T cell proliferation and then induce immune tolerance. IDO catabolism tryptophan to kynurenine, then Kyn products lead to suppression of T effector and tolerance. IDO high-level expression in tissue like intestine so it is important that keep tolerance in this tissue [41,42]. Intestinal LP CD103+ DCs express IDO higher than other DCs and release RA together with IDO, and these molecules are important for drive to Treg in the intestine. The clonal anergy and apoptosis, Fas-mediated cell cycle arrest of T cells can induce by IDO [43,44].

According to Torres., et al. IDO expression increases in the small intestine of CD patients that may be an important part of the mechanism to cause tolerance for dietary antigens. In fact, this increases to try to manage the inflammatory cause by the chronic antigen stimulation [40]. Other studies showed that DCs express suppressive molecules IDO and these molecules have products immunosuppression on [45]. Matteoli., et al. showed IDO in mouse and human intestine is expressed by the tolDCs CD11c + and CD103 + and these DCs lead to differentiate and evolve Treg FOXP3+. IDO also provides a balance between Treg and Th17 in mouse and human lamina propria [34]. A study by Beitnes., et al. showed that infiltration of APC cells with CD163 + CD11c + marker increased in the intestinal tissues of CD patients, but the density of CD103 + DCs decreased [46]. In a study by Tamra Vorobjova., et al. they showed that the density of tolDCs CD103 +, CD207 +, IDO + and CD11c increased in CD patients, especially patients with type 1 diabetes compared to controls [10]. In other studies by Vorobjova., et al. they concluded that the density of tolDCs CD103 +, IDO + was higher in CD patients, especially patients with stage IIIC atrophy, compared with those with healthy small intestinal mucosa [47]. Also, This group showed that the density of DCs CD11c + and Treg cells in CD patients was higher than in patients with gastrointestinal disorders and atopic dermatitis [48]. Although CD causes damages to the small intestine tissue and it seems there are no regulation immune responses, but the immune system (innate and adaptive) by many regulatory mechanisms can control them. Such as DCs CD103+ CD11c+ that they can induce tolerance so they have tolerogenic properties by release TGF-β and RA. These DCs in lymphoid organs can prime T cells and after that migrated to the small intestinal lamina propria and showed immunoregulatory phenotype cells [49,50].

Other suppression factors in tolDCs are inductive NO synthase (iNOS) that they can have tolerogenic functions. In iNOS−/− mice shown that they didn't have tolerogenic profiles in DCs [51]. Holmgen Peterson showed levels of nitrate/nitrite in urine of untreated CD patients.

Citation: Mohammad Rostami-Nejad., et al. “Tolerogenic Dendritic Cell, an Unknown Cell in Celiac Disease”. EC Gastroenterology and Digestive System 7.1 (2020): 01-07.
are high, probably due to increased production of nitric oxide in the inflamed mucosa and an iNOS synthase lead to produce nitric oxide [52]. Overall, all of these molecules are tolDCs cell markers as immune checkpoints and they can regulate the immune response.

**Figure 1:** Celiac disease pathogenesis and regulatory functions of tolerogenic dendritic cells. Gluten peptides in the small intestinal lumen pass into the epithelial barrier via various way: transcellular or paracellular transport mediated by zonulin and retrotransport of secretory IgA via transferrin receptor CD71, deamidated gluten by TG2 in the lamina propria increases binding affinity to HLA-DQ2 or HLA-DQ4, Lamina propria DCs capture deamidated gliadin peptides and present to gluten-specific CD4+ T-cell. Then peptide HLA-DQ complexes active TH1 response determined by IFN-γ, IL-21 and matrix metalloproteinases (MMPs) production, and Th2 secrete cytokines that active and induce clonal expansion of B cell, which drive to (anti-gliadin and anti-tTg2) antibody production plasma cells in genetically predisposed individuals. These antibodies increase the permeability of the epithelial barrier and allow gliadin peptides to access lamina propria. Also, initially the innate immune response active in CD. stress molecules on epithelial cells (MICA/B) upregulate and lead to IL-15 secretion from epithelial cells and can induce immunogenic DCs. Intraepithelial Lymphocytes (IELs) play a central role in inducing apoptosis of intestinal epithelial cells by mechanisms including Fas-ligand, perforin, granzyme B, and NKG2D. Interactions epithelial MICA/B–NKG2D and CD94/NKG2C-HLA-E to IELs activated induce cytotoxic effects on epithelial cells. Tolerogenic dendritic cells contract with various immune cells like effector T cells, B cells that they play in celiac disease pathogenesis: (1) the regulation by co-inhibitory receptor: PDL-1, PDL-2, CTLA-4(CD152) that competes with CD28 for binding to CD80/CD86 receptors on tolDCs surfaces, (2) the regulation by release inhibitory cytokines like IL-10, TGF-β, (3) the regulation by secretion RA, (4) the regulation by produce IDO, iNOS, (5) the regulation by expression of soluble HLA-G.

**Conclusion**

Celiac disease (CD) is immune-dependent chronic small intestinal enteropathy with accumulation dendritic cell induced by gluten in genetically susceptible patients [1]. There are many ways for inhibiting intolerance in autoimmunity disorder like CD, one of the most important is tolerogenic DCs, they can produce various immunomodulatory molecules and effect most types of immune cells such drive
Tolerogenic Dendritic Cell, an Unknown Cell in Celiac Disease

Moreover, several studies shown tolDCs play a pivotal role in CD and control the progression of the immune response that triggers CD and they can regulate immune systems including inhibition mature DC-induced T cell proliferation, IFN-γ and IL-17 secretion and rendered T cells hyporesponsive to further stimulation. also explained that the density of tolDCs cells is higher in the small bowel mucosa of the CD patients with higher-grade CD [10,46,47]. Studies showed that DCs as a player in peripheral tolerance regulated by their activation status, maturation and antigen-presenting capability that control inflammatory and tolerance. tolDCs are critical cells of the immune system that they can regulate the immune response in health and disease. it isn’t known, tolDCs are a specific lineage or development stage [25].

However, despite this regulatory mechanism, this disease progresses. For this reason, other factors are likely to prevent these mechanisms of tolDCs. The role of tolDCs cells in the loss of tolerance to gluten remains poorly understood and needs more investigation. So, they are a possible therapeutic target for CD and discovering of the regulation mechanisms tolerogenic DC will guide new immunotherapy strategies for CD. In this review, we discuss the main phenotypic and functional characteristics of tolDCs in CD. Immune checkpoints tolDCs may be a new and important indicator of the tolerogenic status of DCs, and further research is needed to understand their functional and phenotypic differences between DC subsets.

Bibliography


Citation: Mohammad Rostami-Nejad., et al. “Tolerogenic Dendritic Cell, an Unknown Cell in Celiac Disease”. EC Gastroenterology and Digestive System 7.1 (2020): 01-07.
Tolerogenic Dendritic Cell, an Unknown Cell in Celiac Disease


---