Chapter 2

Mechanisms of Intestinal Tolerance to Dietary Proteins

David Bernardo[1,2], Stella C. Knight[2]

[1] Gastroenterology Unit. Hospital Universitario de La Princesa and Instituto de Investigación Sanitaria Princesa (IIS-IP), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD) Madrid, Spain.

[2] Antigen Presentation Research Group, Imperial College London, Northwick Park and St. Mark's Campus, Mark's Hospital, Harrow, UK.

d.bernardo.ordiz@gmail.com, s.knight@imperial.ac.uk

Doi: http://dx.doi.org/10.3926/oms.250

How to cite this chapter

Bernardo D, Knight SC. *Mechanisms of Intestinal Tolerance to Dietary Proteins*. In Arranz E, Fernández-Bañares F, Rosell CM, Rodrigo L, Peña AS, editors. *Advances in the Understanding of Gluten Related Pathology and the Evolution of Gluten-Free Foods*. Barcelona, Spain: OmniaScience; 2015. p. 105-139.

Abstract

Oral tolerance is defined as the lack of a systemic immune response against antigens previously administered through the gastrointestinal tract. Therefore, in an antigen rich environment such as the intestine, the oral tolerance avoids the development of immune responses against food antigens and the commensal microbiota maintaining immune homeostasis in health. Nevertheless, in some circumstances the immune system fails to develop and/or maintain immune tolerance, triggering an abnormal immune response against the commensals, which occurs in inflammatory bowel diseases and/or against food antigens as evident in celiac disease. In this chapter, we will discuss the unique properties of the immune system in the gastrointestinal tract and study how dendritic cells, the most potent antigen presenting cells, control mechanisms of immune homeostasis in the intestine.

Keywords

Dendritic cells, tolerance, intestine, immunity.

1. Characteristics of the Gastrointestinal Mucosa

The mucosa of the gastrointestinal tract (GIT) is the longest in the human body comprising $100m^2$ (200 times bigger than the skin surface). It consists of a monolayer of epithelial cells specialized in the absorption of water and nutrients and also provides a physical barrier with the external environment.

The intestinal epithelial cells (IEC) constitute the frontier between the external antigen-rich environment [in its lower or distal compartments the GIT carries a total of 10^{12} bacteria per gram of human tissue[1]] and the immune system in the lamina propria (LP) underneath, which comprises the connective tissue between the apical epithelial layer and the inner muscularis mucosae. Barrier function of the IEC is elicited by an array of tight-junctions between the IEC blocking the passage of substances from the lumen. In addition to the epithelial barrier, some IEC like the Goblet cells secrete mucins which constitute the mucus layer on the apical membrane of the IEC. This mucus layer carries a high concentration of anti-microbial defensins, neutrophils and secreted IgA helping to maintain immune homeostasis in the GIT[2,3].

Although IEC are not immune cells, their role in GIT homeostasis and disease cannot be disregarded since some pathologies display increased epithelial gut permeability due to defective or "leaky" tight-junctions. The leakage of food and microbiota antigens through the IEC occurs in some forms of inflammatory bowel disease (IBD) like in Crohn's disease; mucosal exposure to luminal antigens probably provides the basis for sensitivity to food antigens in Crohn's disease, responses to which can then be elicited only through challenge via gut mucosa but not through skin challenge[4]. Patients with celiac disease (CD) have increased epithelial gut permeability too, allowing passage of luminal content antigens including gluten to the LP. The composition of the mucus layer is also altered in CD patients[5,6] as well as the microbiota composition[6-11]. Nevertheless, it remains elusive whether such altered properties of the IEC compartment and the microbiota are cause or consequence of the disease.

2. The Immune System in the Gastrointestinal Tract

Dendritic cells (DC) and macrophages (Mφ) are the main antigen presenting cells (APC) in the GIT and changes in their numbers, phenotype and function have been reported in GIT diseases including CD[12-15]. Nevertheless, DC and Mφ have different functions. DC, the most potent APC, are unique in their capacity to migrate to the lymph nodes to perform antigen presentation and indeed are the only cells which can present antigens to stimulate naïve T-cells[16]. DC, therefore, control the mechanisms of immunity/tolerance in the GIT, maintaining immune tolerance against harmless antigens (mainly derived from the diet and the commensals) whilst also maintaining the capacity to trigger active immune responses, against invading pathogens[17]. Mφ, on the contrary, do not migrate to the lymph nodes and fail to perform antigen presentation to naïve T-cells. However, Mφ provide a first line of phagocytic defence against invading antigens[18] and also modulate effector T-cell responses in the tissues[19,20]. They also help to maintain intestinal tolerance by reducing local inflammation[21] and contributing to epithelial cell renewal[22]. Differential functions at induction and effector sites influence the outcome of the immune responses in the GIT allowing the establishment of regulatory mechanisms required to maintain the properties of the mucosal immune system[23]. Different compartments of the immune system in the GIT can be classified, according to their function and location, into i) sampling; ii) induction; and iii) effector areas.

2.1. Sampling Areas

The sampling areas of the GIT immune system are those areas where antigens are sampled by the DC[24] (Figure 1).

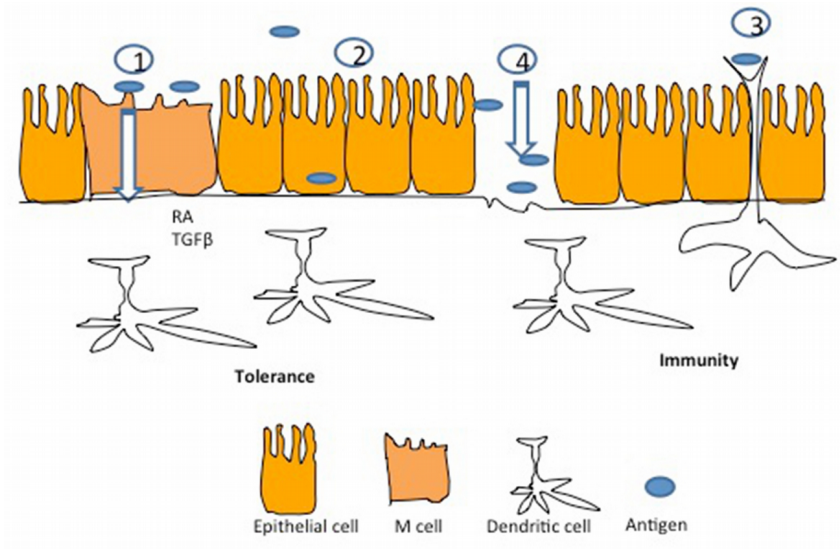

Figure 1. Dendritic cell antigen sampling. DC can sample antigens via (1) M cells at Peyer's Patches, (2) intestinal epithelial cell derived tolerosomes, (3) following direct uptake after sending their veils or dendrites between the epithelial cells or (4) after breakdown of the epithelial integrity. While the first two mechanisms promote immune tolerance, the last two are related with development of active immune responses.

2.1.1. Antigen Transfer Via M Cells at the Peyer's Patches

Peyer's Patches (PP) are lympho-epithelial organs mainly located in the small bowel submucosa. On their apical and external surface PP are covered by a subset of specialized IEC called Microfold or M cells. Such M cells are specialized for direct transfer of particulate antigens from the GIT lumen into tissue beneath the dome of the PP, a compartment rich in DC which will sample the antigens.

2.1.2. Indirect Sampling Via Enterocytes

In contrast to the underdome compartment of the PP, where DC are enriched, DC and other APC such as Mφ are also spread throughout the whole lamina propria of the GIT where they constitute a cell network in intimate contact with the basal membrane of the IEC. In order to maintain the GIT epithelial integrity, IEC can sample the luminal content and secrete antigens onto the basolateral membrane through release of vesicles into the LP where they will be taken up by DC. Such vesicles have been defined as "tolerosomes" as they promote development of tolerogenic responses via LP-DC[25,26]. Nevertheless, DC can also get indirect access to luminal antigens following phagocytosis of apoptotic IEC although in that case they would promote active immune responses against the foreign antigens[24].

2.1.3. Direct Uptake by DC

LP-DC expressing CX3CR1 can extend their veils, or dendrites, between the IEC while establishing tight-junctions in order to maintain the integrity of the epithelial barrier[25] and hence gaining direct access to luminal antigens. Nevertheless, recent evidence has redefined such CX3CR1$^+$ cells as a subset of tissue-resident tolerogenic Mφ[20,28].

2.1.4. Direct Access Following Epithelial Breakdown

When the epithelial integrity is compromised, due to an increase in transepithelial permeability and/or IEC apoptosis (as induced in CD by IL-15 as discussed in other chapters), then the luminal content will have direct access to LP-DC which will trigger an active immune response against the invading pathogens or, in disease, to food or microbiota antigens[24]. Increased epithelial permeability has been associated with several GIT diseases including CD.

2.2. Induction Areas

Following antigen update by the DC, induction areas are those compartments where DC present antigen to naive T-cells. In the GIT, induction areas are comprised of organized lymphoid tissues (including the PP as previously described, the appendix and some lymph nodes) and the mesenteric lymph nodes draining the gut. During antigen presentation DC will not only generate antigen-specific T-cells but will also control their differentiation into pro-inflammatory and/or tolerogenic T-cells

2.3. Effector Areas

Following T-cell priming, antigen-specific effector lymphocytes will migrate back to the GIT to elicit their function at the effector areas in the epithelial compartment and/or the LP.

2.3.1. Intraepihelial Lymphocytes

Intraepitheilal lymphocytes (IEL) constitute a heterogeneous pool of T-cells on the basal membrane of the epithelial and intercalating with the enterocytes. In contrast to immune cells in the LP and non-mucosal immune tissues, IEL constitute a unique mix of lymphocytes. In resting conditions, in healthy controls, human IEL constitute around 20-40 cells per 100 enterocytes in the ileum where they are more frequent. They are characterized by the expression of the CD103 integrin, and most of them (70-90%) have a cytotoxic $CD3^{+}CD4^{-}CD8^{+}$ profile with a classical TCR$\alpha\beta$. Although non-classical TCR$\gamma\delta$ lymphocytes are not very common in other compartments, they represent up to 30% of the total IEL in the GIT being the tissue where they are mainly found. Finally, the IEL compartment comprises a third $CD45^{+}CD3^{-}CD7^{+}$ NK-like cells with cytotoxic capacity[29,30].

2.3.2. Lamina Propria

The LP contains an array of immune cells in addition to fibroblast, smooth muscle cells, lymph and blood vessels. Indeed, although it is not an organized lymphoid tissue, LP of the GIT contains the largest number of immune cells (mainly effector B and T-cells but also DC and Mφ) in the human body.

2.3.2.1. B-cells and IgA

Different B-cell subsets produce different types of immunoglobulins (Ig). IgM/IgG are involved in systemic antibody responses and IgE mediates allergic reactions but the major component of antibody responses in the GIT is IgA. Therefore, IgA is the main Ig in mucosal compartments and the human body secretes over 3g/day. Ig-A promotes a non-aggressive exclusion of pathogens, limiting their access to the IEC, and accumulates in the mucus layer which is also rich in other immune molecules like defensins and bacteriocines, enhancing all together its immune protective function forming the first immune barrier of the GIT[3,31].

2.3.2.2. T-cells

Following antigen presentation, DC determine the outcome (pro-inflammatory/tolerogenic) of the responding antigen-specific T-cells. In both cases, T-cells will migrate from the lymph nodes to the LP where, as the effector site, they will elicit their function (either pro-inflammatory or regulatory).

The role of the *pro-inflammatory lymphocytes* in the GIT has been clearly stated in several intestinal pathologies including CD. Production of pro-inflammatory cytokines by the T-cells compromises the integrity of the epithelial barrier and is also related to structural modifications of the extracellular matrix[32,33]. Production of pro-inflammatory cytokines promote a positive auto- and paracrine feedback for production of chemokines and other pro-inflammatory cytokines which exacerbate the immune response and the

tissue injury. Generation of gluten-specific pro-inflammatory T-cells following antigen presentation by DC is the ultimate cause of CD pathogenesis.

Regulatory T-cells, are $CD4^+$ lymphocytes characterized by the expression of high levels of CD25 in which activity is controlled by the expression of the FoxP3 transcription factor. In contrast to pro-inflammatory T-cells, regulatory T-cells mediate immune homeostasis. Some regulatory T cells produce large quantities of regulatory cytokines (mainly IL-10). As a consequence, regulatory T-cells block the proliferation of pro-inflammatory T-cells, inhibit the production of pro-inflammatory cytokines and cooperate with local B-cells to enhance their production of IgA[34]. However, T-cell properties are dynamic[35-37] so their discrimination into pro-inflammatory and regulatory T-cells may be an oversimplification caused by cell density and/or cell contact inhibition[38].

In summary, the immune system in the GIT promotes immune tolerance against the encountered antigens, mainly derived from commensals and food, via GIT-DC which promote the generation of antigen specific Ig-A secreting B-cells and regulatory T-cells which together maintain immune homeostasis. Nevertheless, in some pathologies like CD, DC "are confused" and fail to recognize gluten as a harmless dietary antigen. When that happens, DC promote the development of gluten-specific pro-inflammatory T-cells which control progression of the disease. In the following sections, we will therefore discuss the properties of GIT-DC and try to understand some of the causes which may cause their malfunction in CD.

3. Dendritic Cells Biology

DC are potent APC. In contrast to other APCs such as B-lymphocytes (excluding already activated B cells) or Mφ, DCs are unique in their capacity to initiate a primary immune response by stimulating naïve T-cells; they also control the outcome (tolerogenic or proinflammatory) of the immune responses[16,39-41].

DC precursors migrate from the bone marrow to virtually all tissues in the body, including the mucosa in the GIT. Once in the tissues, DC become sentinels and sensors of the immune system. DC are sentinels as they are highly effective capturing and processing antigens[42,43] and hence sampling the surrounding environment. DC are also sensors given their capacity to discriminate the nature (harmful/harmless) of the sampled antigen via their high expression of pattern recognition receptor (PRR) molecules [including Toll-like receptors (TLRs)[44-46]] but also given their capacity to become activated in the presence of an innate immune stress (e.g. pro-inflammatory cytokines or oxidative stress)[47,48]. Therefore, DC occupy the interface between the innate and the highly specialized antigen-specific adaptive immune system.

When DC capture a "danger antigen", as recognized via their PRR and/or following maturation induced by an innate immune response, tissue DC lose their high antigen-processing capacity and migrate to secondary lymphoid organs in a CCR7-dependent manner[49,50] in a process of maturation which will promote their capacity to present the antigens to T-cells. Within the lymph nodes, mature DC will deliver three different signals to the naïve T-cells which will control their differentiation into antigen-specific pro-inflammatory T-cells. Such signals include i) an increased expression of the processed antigens on the surface of the HLA-II molecules; ii) increased expression of co-stimulatory molecules CD80(B7.1)/CD86(B7.2) (T-cell CD28/CTLA4 ligands) and/or CD40 (T-cell CD40L ligand); and iii) increased capacity to produce pro-inflammatory cytokines, like IL-12[51,52]. Therefore, lymph node mature DC have lost their antigen-capturing ability but are efficient for antigen presentation and lymphocyte stimulation controlling their differentiation into antigen-specific effector (pro-inflammatory) T-cells. However, DC can also drive development of non-inflammatory (tolerogenic or regulatory) lymphocytes if, at the time of the antigen presentation, they display a decreased expression of the first two signals coupled with an increased capacity to produce regulatory cytokines, like IL-10. In this manner, DC control the development of pro-inflammatory responses against foreign

harmful antigens whilst maintaining immune tolerance against harmless antigens.

3.1. Dendritic Cells and Migration Markers: Connecting Induction and Effector Areas

Antigen specific B- and T-cells express tissue-specific homing markers which control their migration back to the target tissues where the antigen is found. Lymphocytes migrating back to the GIT express on their surface the $\alpha 4\beta 7$ integrin[53] and/or the chemokine receptor CCR9[54]. The ligand for the $\alpha 4\beta 7$ heterodimer is the MAdCAM-1 molecule which is expressed by endothelial cells in the LP post-capillary venules of both the small and large bowels[55,56]. On the contrary, the ligand for CCR9 is the CCL25/TECK chemoattractant expressed by small-bowel epithelial cells[57,58]; there is a gradient of expression which is maximal at the proximal end of the small bowel and gradually decreases in the ileum to become undetectable in the colon[59]. Therefore, while $\alpha 4\beta 7^+$ lymphocytes have general mucosal tropism, those co-expressing $CCR9^+$ are specifically directed towards the small intestine, like pro-inflammatory gluten-specific T-cells in CD.

T-cell expression of such homing markers is controlled by DC. Thus, DC not only control the outcome (proinflammatory/toregonic) of the immune responses but also the location of that response via homing marker imprinting on antigen-specific lymphocytes[60]. Prior to stimulation, naïve T-cells express migration markers that lead them to lymphoid tissues[61]. DC entering tissues from the blood gain specificity induced by their tissue of residence. DC within the tissues, particularly after exposure to antigens, will migrate to the draining lymph nodes and deliver a fourth signal to the T-cells as they induce the expression of homing or migration markers on the responding lymphocytes[62-65]. Therefore, antigen specific responding lymphocytes are directed back to the target tissues where the antigens were found so that immune responses are performed in a compartmentalized tissue-specific way. The mechanisms through which DC induce the expression of tissue-specific homing markers on responding T-cells remain elusive but seem

to involve –among other components– fat soluble vitamins like vitamin A and D. The 25-OHD molecule (generated in the skin following the ultraviolet light-dependent activation of vitamin D) induces the expression of skin-homing markers on DC and hence on the T cells they stimulate T-cells[66]. Retinoic acid (RA), which is a metabolite of dietary vitamin A, induces the expression of gut-homing markers $\alpha 4\beta 7$ and/or CCR9 on DC which then stimulate T-cells with similar properties[62,65,67,68]. DC from the GIT –but not from other tissues-possess the enzymatic machinery necessary to synthesize RA[69-71] providing the mechanism by which GIT-DC gain gut specificity that will then control the migration of the antigen specific lymphocytes back to the GIT effector compartments[62,65,68]. Moreover, DC themselves also express tissue-specific homing markers which vary according to their location[65]. Circulating myeloid DC from CD patients (both untreated at diagnosis and after clinical remission following gluten-free diet) display an altered expression of migration markers with very high expression of CCR9[72] suggesting an increased small bowel migratory capacity which may correlate with a higher infiltration of DCs in target tissues[12]. Nevertheless, the mechanisms producing changes in homing capacity of circulating DC are unknown since it is generally accepted that DC normally die within lymph nodes and do not recirculate[73].

4. Dendritic Cells and Oral Tolerance

GIT-DC are exposed to a large amount of foreign, but harmless, antigens mainly derived from the commensal bacteria and the food. Therefore, in contrast to DC from other tissues, GIT-DC promote the immune tolerance against such antigens[74-76].

The lower immunogenic capacity of intestinal DC results from a number of factors. One of them is that GIT-DC have lower expression of PRRs -including TLR molecules-[77] which confers on them a lower capacity to recognize bacterial antigens in such microbiota-rich environment. In addition to decreased TLR expression, GIT-DC also display an immature phenotype as compared with DC

from other tissues; they have lower expression of both HLA-II molecules and surface co-stimulatory molecules, increased phagocytic capacity and higher capacity to produce regulatory cytokines such as IL-10[77-79]. Such a tolerogenic profile confers GIT-DC with a reduced stimulatory capacity when compared with DC from other tissues[65] which is key in preventing inflammatory processes in the absence of invading pathogens. In addition to their decreased stimulatory capacity, GIT-DC also promote the differentiation of both T-cells with antigen-specific regulatory properties and IgA-secreting B-cells which mediate immune tolerance in the GIT[80-84]. Last, but not least, GIT-DC also imprint gut-homing markers ($\alpha 4\beta 7$ and/or CCR9) on both Ig-A secreting B-cells and regulatory T-cells[81,85] so trafficking of such tolerogenic T-cells and IgA secreting B-cells is restricted to the gastrointestinal compartment. GIT-DC tolerogenic properties are dependent on RA which is essential for intestinal immune tolerance; it is only intestinal DCs (but not DC from other tissues) that possess the enzymatic machinery necessary to convert vitamin A into RA[69-71] and therefore provide the capacity to generate gut-homing regulatory T-cells and IgA-secreting B-cells[81,85-89]. Nevertheless, GIT-also maintains the capacity to trigger an active immune response against invading pathogens. Given that plasticity to maintain immune tolerance against food/commensals while triggering active immune responses against invading pathogens, it has been recently suggested that the GIT contains different DC subsets, each of them being responsible for different outcomes of the immune responses as discussed in the next section.

4.1. DC Subsets in the GIT

Intestinal DCs were originally classified into two mutually exclusive subsets: tolerogenic ($CD103^+$) and proinflammatory ($CX3CR1^+$) DC which respectively control immune tolerance against food and commensals or trigger immune responses against invading pathogens respectively[90-92]. Tolerogenic $CD103^+$DC, are derived from newly arrived DC, have the capacity to migrate to the lymph nodes in a CCR7 dependent manner, and possess the machinery (enzyme RALDH2) necessary to metabolize vitamin A and generate RA generation which mediates several GIT-DC properties. On the contrary, $CX3CR1^+$DC are

derived from newly arrived monocytes and lack both the enzymatic machinery to synthesize RA and the capacity to migrate to the lymph nodes; they would elicit a pro-inflammatory effect against invading pathogens.

4.1.1. CX3CR1$^+$ APC

CX3CR1$^+$DC were originally identified as the GIT-DC subset with capacity to send their dendrites through the IEC, establishing tight-junctions with them, and accessing luminal antigens[25]. Although originally defined as DC, CX3CR1 is virtually absent on colonic DC and CX3CR1$^+$ APC have been recently redefined as Mφ[20,28,93]. Their pro-inflammatory role has also been revisited given their capacity to expand T-cells with regulatory properties on an IL-10 dependent manner[20,94]. Moreover, CX3CR1$^+$Mφ also contribute to immune homeostasis given their capacity to extend their projections between the IEC and migrate towards the lumen in the presence of an infection while becoming loaded with bacterial antigens, thus limiting their access the LP[18,95].

4.1.2. CD103$^+$ DC

Intestinal CD103$^+$ DC can migrate to the lymph nodes, in a CCR7 dependent manner. Within them, the subset co-expressing CD11b$^+$ (murine analog of human CD1c, which identifies type 1 myeloid DC) is unique to the gut controlling the immune tolerance mainly via retinaldehyde dehydrogenase type 2 (RALDH-2) required to generate retinoic acid which mediates several GIT-DC properties[28,96,97].

CD103$^+$DC are decreased in the duodenum of CD patients[14] suggesting that they are related with the lack of oral tolerance against dietary gluten in such patients. However, most our knowledge about the tolerogenic GIT CD103$^+$DC subset have been obtained from murine models which, although essential to further our understanding on DC biology, may not always be translated into the human context[93,98]. Thus, although a majority of human GIT-DC have a regulatory profile[65,77,78,99] that is not restricted to the CD103$^+$ population which are not the main DC subset in the human GIT[14,93,100]. RALDH2 expression is

not restricted to human $CD103^+$ subset as it is also found on $CD103^-$ DC and even Mφ[100]. Moreover, recent evidence suggests that the system is more dynamic that originally described; "tolerogenic" $CD103^+CD11b^+$DC can also drive pro-inflammatory Th17 responses[28], $CD103^-$DC can also generate RA and migrate to the lymph nodes[101] and, finally, DC subsets and function also depend on the mouse strain and GIT location[102] proving GIT-DC plasticity.

Together, and although different DC subsets may exist in the GIT, it seems that the distinction between different DC subsets with different functions may be an oversimplification; DC properties are dynamic and depend on the surrounding microenvironment in which they are found.

4.2. Intestinal DC Plasticity

Tissue DC express different migration markers which are modulated by the local microenvironment[65,103] as DC acquire tissue-specific migration markers and the capacity to imprint them on lymphocytes they stimulate[62,65,68,104]. However, the tissue microenvironment does not only modulate DC homing marker expression but also their maturation status as innate immune factors induce DC maturation. In the absence of inflammation, GIT-DC acquire a regulatory profile following exposure to various "sedative" signals mainly secreted by the IEC[105-108] including thymic stromal lymphopoietin (TSLP), regulatory cytokines like TGF-β and IL-10 and RA[65,81,107,108] (Figure 2). Under such a sedative environment, and in the absence of external immune insults, GIT-DC acquire an immature phenotype characterized by decreased expression of PRR, but also of HLA-Class II molecules, co-stimulatory molecules and also an increased capacity to secrete regulatory cytokines. Given their capacity to metabolize vitamin A and generate RA, GIT-DC in such a calming environment will generate antigen-specific gut-homing T-cells with regulatory function and IgA-secreting B-cells which will in turn promote and maintain the mechanisms of immune tolerance against dietary and commensal antigens.

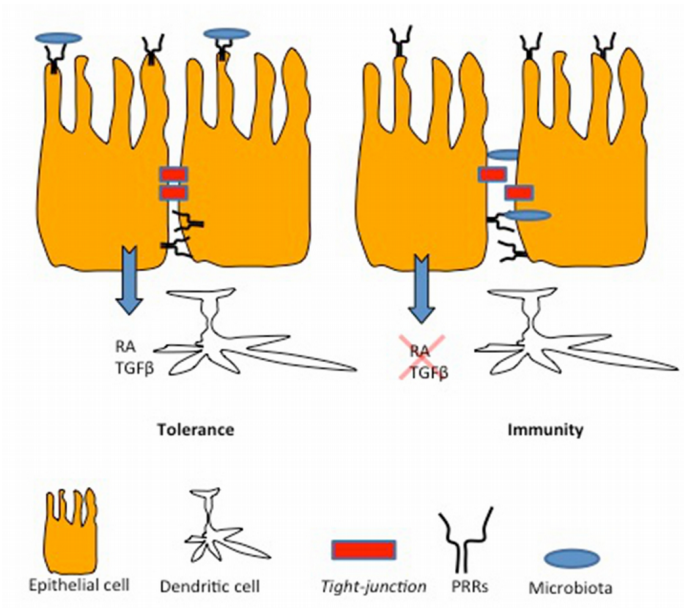

Figure 2. Epithelial cells and dendritic cell crosstalk.

Left: In resting conditions, in healthy controls, intestinal epithelial cells (IEC) recognize microbiota antigens in their apical membrane via pattern recognition receptors (PRR). When that happens, IEC secrete TGF-β and retinoic acid (RA) hence modulating lamina propria dendritic cells towards a tolerogenic phenotype.

Right: In the presence of invading bacteria, tight-junction integrity is compromised and pathogens get access through being recognized by PRR located on the basolateral membrane of the IEC. In this setting, IEC block the secretion of inhibitory signals and, conversely, of DC modulation towards tolerance.

The intestinal immune system is, however, dynamic. In the presence of danger signals its regulatory profile disappears as IEC stop secreting "sedative" signals. This is partly due to the fact that IEC can recognize the presence of invading bacteria. IEC are programmed to secrete TGF-β and RA when recognizing bacteria in their apical membrane by means of their PRRs; however, in the presence of invading bacteria tight junction integrity is affected so pathogens access through and are recognized by the PRRs located on the basolateral membrane of the IEC[109-112]. In this setting, IEC block the secretion of inhibitory signals and, conversely, of DC modulation towards

tolerance. Furthermore, the presence of an innate immune response against invading bacteria involves the secretion of different pro-inflammatory cytokines and/or oxygen reactive species with the ability to induce DC maturation[47,48]. Under such conditions, DC recognize captured antigens as invading pathogens, blocking immune tolerance and triggering active immune responses (Figure 2). This capacity of DCs to respond rapidly and efficiently to their microenvironment grants them the ability to control the immune system and the balance between immunity and tolerance. Nevertheless, the system is not perfect and factors altering the balance can lead to malfunctioning DC as in CD.

5. Dendritic Cells in Celiac Disease

DC maintain immune homeostasis in the GIT while in CD, they trigger an antigen-specific immune response against dietary gluten. DC themselves are the cell type expressing the HLA-DQ2/8 molecules (the main susceptibility genes in CD), a type of HLA-II molecule unique in their capacity to accommodate gluten antigens and perform antigen presentation. Nevertheless, the reason why gluten is recognized as a harmful antigen by DC remains elusive. Increased expression of TLR molecules on GIT-DC and MyD88 signalling has been reported in some pathologies like IBD[77,113]. Although GIT-DC have not been extensively studied in CD, tissue PRR expression is altered in the celiac mucosa[10,114,115] and gluten antigens are also recognized in a MyD88 dependent manner[116,117] so a potential role of PRR on gluten recognition in CD cannot be discarded.

Another possibility, however, suggests that DC do not recognize gluten as harmful antigen directly but only as a consequence of an innate immune response triggered in the GIT. As discussed in other chapters of this book, gluten antigens have a dual effect on the GIT mucosa of the CD patients as it triggers an innate immune response followed by a secondary antigen specific adaptive immune response. The second is triggered by the DC, which, as previously discussed, fail to recognize gluten as a harmless dietary antigen.

The reason for DC "confusion" could be a consequence of the first non-specific innate immune response. Such innate response[118] is characterized by the production of IL-15 by IEC in a NF-kB dependent manner following gluten recognition[119,120]. IL-15 has a direct effect disrupting the epithelial barrier as it increases tight-junction permeability[121,122] and induces apoptosis of IEC[123-126]. Under such immunological stress, IEC stop secreting their sedative signals (Figure 2). IL-15 also has the capacity to activate DC directly and the DC would then mature towards a pro-inflammatory phenotype (Figure 3). Gluten-induced IL-15 production by IEC is central in the first steps of CD pathogenesis and it also elicits co-adjuvant effects with RA exacerbating inflammatory responses to dietary antigens[127]. Therefore, gluten antigens sampled by DC are recognized as harmful and DC promote the differentiation of gluten-specific gut-homing pro-inflammatory T-cells; once back in the effector tissue (lamina propria) these T- cells will promote development and progression of the disease. DC, are therefore responsible for the incapacity of CD patients to establish immune tolerance against ingested gluten proteins; instead, they cause development of antigen-specific immune response.

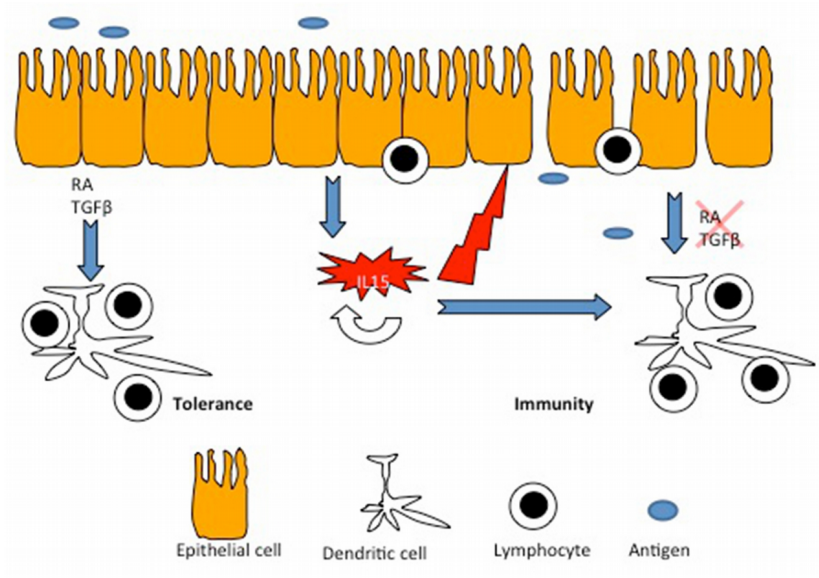

Figure 3. Dendritic cells and celiac disease. In resting condition, in healthy controls, intestinal epithelial cells (IEC) secrete sedative signals, including TGF-β and retinoic acid (RA), which modulate lamina propria dendritic cells (DC) towards a tolerogenic phenotype. In celiac disease, dietary gluten antigens induce an innate immune response characterized by IL-15 production by IEC. Pro-inflammatory IL-15 increases tight-junction permeability and induces IEC apoptosis. In such stressful environment, IEC stop the secretion of the sedative signals and therefore of DC modulation towards tolerance. Pro-inflammatory cytokines like IL-15 also have a direct maturation effect on DC. As a consequence, gluten antigens reaching to the lamina propria are now recognized as harmful so DC trigger the development of an antigen-specific immune response and hence the development of celiac disease pathogenesis.

References

1. Hooper LV, Midtvedt T, Gordon JI. *How host-microbial interactions shape the nutrient environment of the mammalian intestine.* Annu Rev Nutr. 2002; 22: 283-307.

   http://dx.doi.org/10.1146/annurev.nutr.22.011602.092259
   PMid:12055347

2. Hooper LV, Littman DR, Macpherson AJ. *Interactions between the microbiota and the immune system.* Science. 2012; 336: 1268-73.

   http://dx.doi.org/10.1126/science.1223490
   PMid:22674334

3. Shan M, Gentile M, Yeiser JR, Walland AC, Bornstein VU, Chen K et al. *Mucus enhances gut homeostasis and oral tolerance by delivering immunoregulatory signals.* Science. 2013; 342: 447-53.

   http://dx.doi.org/10.1126/science.1237910
   PMid:24072822 PMCid:PMC4005805

4. Van Den Bogaerde J, Cahill J, Emmanuel AV, Vaizey CJ, Talbot IC, Knight SC et al. *Gut mucosal response to food antigens in Crohn's disease.* Aliment Pharmacol Ther. 2002; 16: 1903-15.

   http://dx.doi.org/10.1046/j.1365-2036.2002.01360.x
   PMid:12390099

5. Ciacci C, Di Vizio D, Seth R, Insabato G, Mazzacca G, Podolsky DK et al. *Selective reduction of intestinal trefoil factor in untreated coeliac disease.* Clin Exp Immunol. 2002; 130: 526-31.

   http://dx.doi.org/10.1046/j.1365-2249.2002.02011.x
   PMid:12452845 PMCid:PMC1906543

6. Forsberg G, Fahlgren A, Hörstedt P, Hammarström S, Hernell O, Hammarström ML. *Presence of bacteria and innate immunity of intestinal epithelium in childhood celiac disease.* Am J Gastroenterol. 2004; 99: 894-904.

   http://dx.doi.org/10.1111/j.1572-0241.2004.04157.x
   PMid:15128357

7. Sánchez E, Nadal I, Donat E, Ribes-Koninckx C, Calabuig M, Sanz Y. *Reduced diversity and increased virulence-gene carriage in intestinal enterobacteria of coeliac children.* BMC Gastroenterol. 2008; 8: 50.

   http://dx.doi.org/10.1186/1471-230X-8-50
   PMid:18983674 PMCid:PMC2615025

8. Collado MC, Donat E, Ribes-Koninckx C, Calabuig M, Sanz Y. *Specific duodenal and faecal bacterial groups associated with paediatric coeliac disease.* J Clin Pathol. 2009; 62: 264-9.

http://dx.doi.org/10.1136/jcp.2008.061366
PMid:18996905

9. Nistal E, Caminero A, Herrán AR, Arias L, Vivas S, de Morales JM et al. *Differences of small intestinal bacteria populations in adults and children with/without celiac disease: effect of age, gluten diet, and disease.* Inflamm Bowel Dis. 2012; 18: 649-56.

http://dx.doi.org/10.1002/ibd.21830
PMid:21826768

10. Cheng J, Kalliomäki M, Heilig HG, Palva A, Lähteenoja H, de Vos WM et al. *Duodenal microbiota composition and mucosal homeostasis in pediatric celiac disease.* BMC Gastroenterol. 2013; 13: 113.

http://dx.doi.org/10.1186/1471-230X-13-113
PMid:23844808 PMCid:PMC3716955

11. Caminero A, Herrán AR, Nistal E, Pérez-Andrés J, Vaquero L, Vivas S et al. *Diversity of the cultivable human gut microbiome involved in gluten metabolism: isolation of microorganisms with potential interest for coeliac disease.* FEMS Microbiol Ecol. 2014.

12. Ráki M, Tollefsen S, Molberg Ø, Lundin KE, Sollid LM, Jahnsen FL. *A unique dendritic cell subset accumulates in the celiac lesion and efficiently activates gluten-reactive T cells.* Gastroenterology. 2006; 131: 428-38.

http://dx.doi.org/10.1053/j.gastro.2006.06.002
PMid:16890596

13. Di Sabatino A, Pickard KM, Gordon JN, Salvati V, Mazzarella G, Beattie RM et al. *Evidence for the role of interferon-alfa production by dendritic cells in the Th1 response in celiac disease.* Gastroenterology. 2007; 133: 1175-87.

http://dx.doi.org/10.1053/j.gastro.2007.08.018
PMid:17919493

14. Beitnes AC, Ráki M, Lundin KE, Jahnsen J, Sollid LM, Jahnsen FL. *Density of CD163+ CD11c+ dendritic cells increases and CD103+ dendritic cells decreases in the coeliac lesion.* Scand J Immunol. 2011; 74: 186-94.

http://dx.doi.org/10.1111/j.1365-3083.2011.02549.x
PMid:21392045

15. Beitnes AC, Ráki M, Brottveit M, Lundin KE, Jahnsen FL, Sollid LM. *Rapid accumulation of CD14+CD11c+ dendritic cells in gut mucosa of celiac disease after in vivo gluten challenge.* PLoS One. 2012; 7: e33556.

http://dx.doi.org/10.1371/journal.pone.0033556
PMid:22438948 PMCid:PMC3306402

16. Banchereau J, Steinman RM. *Dendritic cells and the control of immunity.* Nature. 1998; 392: 245-52.

http://dx.doi.org/10.1038/32588
PMid:9521319

17. Pabst O, Mowat AM. *Oral tolerance to food protein.* Mucosal Immunol. 2012; 5: 232-9.

http://dx.doi.org/10.1038/mi.2012.4
PMid:22318493 PMCid:PMC3328017

18. Arques JL, Hautefort I, Ivory K, Bertelli E, Regoli M, Clare S et al. *Salmonella induces flagellin- and MyD88-dependent migration of bacteria-capturing dendritic cells into the gut lumen.* Gastroenterology. 2009; 137: 579-87.

http://dx.doi.org/10.1053/j.gastro.2009.04.010
PMid:19375423

19. Platt AM, Mowat AM. *Mucosal macrophages and the regulation of immune responses in the intestine.* Immunol Lett. 2008; 119: 22-31.

http://dx.doi.org/10.1016/j.imlet.2008.05.009
PMid:18601952

20. Hadis U, Wahl B, Schulz O, Hardtke-Wolenski M, Schippers A, Wagner N et al. *Intestinal tolerance requires gut homing and expansion of FoxP3+ regulatory T cells in the lamina propria.* Immunity. 2011; 34: 237-46.

http://dx.doi.org/10.1016/j.immuni.2011.01.016
PMid:21333554

21. Jiang C, Ting AT, Seed B. *PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines.* Nature. 1998; 391: 82-6.

http://dx.doi.org/10.1038/35154

22. Pull SL, Doherty JM, Mills JC, Gordon JI, Stappenbeck TS. *Activated macrophages are an adaptive element of the colonic epithelial progenitor niche necessary for regenerative responses to injury.* Proc Natl Acad Sci USA. 2005; 102: 99-104.

http://dx.doi.org/10.1073/pnas.0405979102
PMid:15615857 PMCid:PMC544052

23. Macdonald TT, Monteleone G. *Immunity, inflammation, and allergy in the gut.* Science. 2005; 307: 1920-5.

http://dx.doi.org/10.1126/science.1106442
PMid:15790845

24. Ng SC, Kamm MA, Stagg AJ, Knight SC. *Intestinal dendritic cells: their role in bacterial recognition, lymphocyte homing, and intestinal inflammation.* Inflamm Bowel Dis. 2010; 16: 1787-807.

http://dx.doi.org/10.1002/ibd.21247
PMid:20222140

25. Rescigno M, Urbano M, Valzasina B, Francolini M, Rotta G, Bonasio R et al. *Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria.* Nat Immunol. 2001; 2: 361-7.

http://dx.doi.org/10.1038/86373
PMid:11276208

26. Karlsson M, Lundin S, Dahlgren U, Kahu H, Pettersson I, Telemo E. "*Tolerosomes" are produced by intestinal epithelial cells.* Eur J Immunol. 2001; 31: 2892-900.

http://dx.doi.org/10.1002/1521-4141(2001010)31:10<2892::AID-IMMU2892>3.0.CO;2-I

27. Ostman S, Taube M, Telemo E. *Tolerosome-induced oral tolerance is MHC dependent.* Immunology. 2005; 116: 464-76.

http://dx.doi.org/10.1111/j.1365-2567.2005.02245.x

28. Persson EK, Scott CL, Mowat AM, Agace WW. *Dendritic cell subsets in the intestinal lamina propria: ontogeny and function.* Eur J Immunol. 2013; 43: 3098-107.

http://dx.doi.org/10.1002/eji.201343740
PMid:23966272 PMCid:PMC3933733

29. Abadie V, Discepolo V, Jabri B. *Intraepithelial lymphocytes in celiac disease immunopathology.* Semin Immunopathol. 2012; 34: 551-66.

http://dx.doi.org/10.1007/s00281-012-0316-x
PMid:22660791

30. Meresse B, Malamut G, Cerf-Bensussan N. *Celiac disease: an immunological jigsaw.* Immunity. 2012; 36: 907-19.

http://dx.doi.org/10.1016/j.immuni.2012.06.006
PMid:22749351

31. Suzuki K, Ha SA, Tsuji M, Fagarasan S. *Intestinal IgA synthesis: a primitive form of adaptive immunity that regulates microbial communities in the gut.* Semin Immunol. 2007; 19: 127-35.

http://dx.doi.org/10.1016/j.smim.2006.10.001
PMid:17161619

32. Nilsen EM, Jahnsen FL, Lundin KE, Johansen FE, Fausa O, Sollid LM et al. *Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease.* Gastroenterology. 1998; 115: 551-63.

http://dx.doi.org/10.1016/S0016-5085(98)70134-9

33. Forsberg G, Hernell O, Melgar S, Israelsson A, Hammarström S, Hammarström ML. *Paradoxical coexpression of proinflammatory and down-regulatory cytokines in intestinal T cells in childhood celiac disease.* Gastroenterology. 2002; 123: 667-78.

http://dx.doi.org/10.1053/gast.2002.35355
PMid:12198691

34. Mills KH. *Regulatory T cells: friend or foe in immunity to infection?* Nat Rev Immunol. 2004; 4: 841-55.

http://dx.doi.org/10.1038/nri1485
PMid:15516964

35. Thorpe PE, Knight SC. *Microplate culture of mouse lymph node cells. I. Quantitation of responses to allogeneic lymphocytes endotoxin and phytomitogens.* J Immunol Methods. 1974; 5: 387-404.

http://dx.doi.org/10.1016/0022-1759(74)90022-2

36. Farrant J, Knight SC. *Help and suppression by lymphoid cells as a function of cellular concentration.* Proc Natl Acad Sci USA. 1979; 76: 3507-10.

http://dx.doi.org/10.1073/pnas.76.7.3507
PMid:158761 PMCid:PMC383856

37. Knight SC. *Control of lymphocyte stimulation in vitro: "help" and "suppression" in the light of lymphoid population dynamics.* J Immunol Methods. 1982; 50: R51-63.

http://dx.doi.org/10.1016/0022-1759(82)90297-6

38. Bernardo D, Al-Hassi HO, Mann ER, Tee CT, Murugananthan AU, Peake ST et al. *T-cell proliferation and forkhead box P3 expression in human T cells are dependent on T-cell density: physics of a confined space?* Hum Immunol. 2012; 73: 223-31.

http://dx.doi.org/10.1016/j.humimm.2011.12.017
PMid:22248741

39. Knight SC, Balfour BM, O'Brien J, Buttifant L, Sumerska T, Clarke J. *Role of veiled cells in lymphocyte activation.* Eur J Immunol. 1982; 12: 1057-60.

http://dx.doi.org/10.1002/eji.1830121214
PMid:7160425

40. Knight SC, Mertin J, Stackpoole A, Clark J. *Induction of immune responses in vivo with small numbers of veiled (dendritic) cells.* Proc Natl Acad Sci USA. 1983; 80: 6032-5.

http://dx.doi.org/10.1073/pnas.80.19.6032
PMid:6604279 PMCid:PMC534354

41. Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ et al. *Immunobiology of dendritic cells.* Annu Rev Immunol. 2000; 18: 767-811.

http://dx.doi.org/10.1146/annurev.immunol.18.1.767
PMid:10837075

42. Jiang W, Swiggard WJ, Heufler C, Peng M, Mirza A, Steinman RM et al. *The receptor DEC-205 expressed by dendritic cells and thymic epithelial cells is involved in antigen processing.* Nature. 1995; 375: 151-5.

http://dx.doi.org/10.1038/375151a0
PMid:7753172

43. Sallusto F, Cella M, Danieli C, Lanzavecchia A. *Dendritic cells use macropinocytosis and the mannose receptor to concentrate macromolecules in the major histocompatibility complex class II compartment: downregulation by cytokines and bacterial products.* J Exp Med. 1995; 182: 389-400.

http://dx.doi.org/10.1084/jem.182.2.389
PMid:7629501

44. Kabelitz D, Wesch D, Oberg HH. *Regulation of regulatory T cells: role of dendritic cells and toll-like receptors.* Crit Rev Immunol. 2006; 26: 291-306.

http://dx.doi.org/10.1615/CritRevImmunol.v26.i4.10
PMid:17073555

45. Benko S, Magyarics Z, Szabó A, Rajnavölgyi E. *Dendritic cell subtypes as primary targets of vaccines: the emerging role and cross-talk of pattern recognition receptors.* Biol Chem. 2008; 389: 469-85.

http://dx.doi.org/10.1515/BC.2008.054
PMid:18953714

46. Granucci F, Zanoni I, Ricciardi-Castagnoli P. *Central role of dendritic cells in the regulation and deregulation of immune responses.* Cell Mol Life Sci. 2008; 65: 1683-97.

http://dx.doi.org/10.1007/s00018-008-8009-2
PMid:18327662

47. Reis e Sousa C. *Activation of dendritic cells: translating innate into adaptive immunity.* Curr Opin Immunol. 2004; 16: 21-5.

http://dx.doi.org/10.1016/j.coi.2003.11.007
PMid:14734106

48. Perera PY, Lichy JH, Waldmann TA, Perera LP. *The role of interleukin-15 in inflammation and immune responses to infection: implications for its therapeutic use.* Microbes Infect. 2012; 14: 247-61.

http://dx.doi.org/10.1016/j.micinf.2011.10.006
PMid:22064066 PMCid:PMC3270128

49. Sallusto F, Schaerli P, Loetscher P, Schaniel C, Lenig D, Mackay CR et al. *Rapid and coordinated switch in chemokine receptor expression during dendritic cell maturation.* Eur J Immunol. 1998; 28: 2760-9.

http://dx.doi.org/10.1002/(SICI)1521-4141(199809)28:09<2760::AID-IMMU2760>3.0.CO;2-N

50. Banchereau J. *The long arm of the immune system.* Sci Am. 2002; 287: 52-9.

http://dx.doi.org/10.1038/scientificamerican1102-52
PMid:12395726

51. Cella M, Scheidegger D, Palmer-Lehmann K, Lane P, Lanzavecchia A, Alber G. *Ligation of CD40 on dendritic cells triggers production of high levels of interleukin-12 and enhances T cell stimulatory capacity: T-T help via APC activation.* J Exp Med. 1996; 184: 747-52.

http://dx.doi.org/10.1084/jem.184.2.747
PMid:8760829

52. Cella M, Engering A, Pinet V, Pieters J, Lanzavecchia A. Inflammatory stimuli induce accumulation of MHC class II complexes on dendritic cells. Nature. 1997; 388: 782-7.

http://dx.doi.org/10.1038/42030
PMid:9285591

53. Lefrançois L, Parker CM, Olson S, Muller W, Wagner N, Schön MP et al. *The role of beta7 integrins in CD8 T cell trafficking during an antiviral immune response.* J Exp Med. 1999; 189: 1631-8.

http://dx.doi.org/10.1084/jem.189.10.1631
PMid:10330442 PMCid:PMC2193647

54. Butcher EC, Williams M, Youngman K, Rott L, Briskin M. *Lymphocyte trafficking and regional immunity.* Adv Immunol. 1999; 72: 209-53.

http://dx.doi.org/10.1016/S0065-2776(08)60022-X

55. Berlin C, Berg EL, Briskin MJ, Andrew DP, Kilshaw PJ, Holzmann B et al. *Alpha 4 beta 7 integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1.* Cell. 1993; 74: 185-95.

http://dx.doi.org/10.1016/0092-8674(93)90305-A

56. Berg EL, McEvoy LM, Berlin C, Bargatze RF, Butcher EC. *L-selection-mediated lymphocyte rolling on MAdCAM-1.* Nature. 1993; 366: 695-8.

http://dx.doi.org/10.1038/366695a0
PMid:7505053

57. Wurbel MA, Philippe JM, Nguyen C, Victorero G, Freeman T, Wooding P et al. *The chemokine TECK is expressed by thymic and intestinal epithelial cells and attracts double- and single-positive thymocytes expressing the TECK receptor CCR9.* Eur J Immunol. 2000; 30: 262-71.

http://dx.doi.org/10.1002/1521-4141(200001)30:1<262::AID-IMMU262>3.0.CO;2-0

58. Johansson-Lindbom B, Agace WW. *Generation of gut-homing T cells and their localization to the small intestinal mucosa.* Immunol Rev. 2007; 215: 226-42.

http://dx.doi.org/10.1111/j.1600-065X.2006.00482.x
PMid:17291292

59. Ericsson A, Kotarsky K, Svensson M, Sigvardsson M, Agace W. *Functional characterization of the CCL25 promoter in small intestinal epithelial cells suggests a regulatory role for caudal-related homeobox (Cdx) transcription factors.* J Immunol. 2006; 176: 3642-51.

http://dx.doi.org/10.4049/jimmunol.176.6.3642
PMid:16517733

60. Hart AL, Ng SC, Mann E, Al-Hassi HO, Bernardo D, Knight SC. *Homing of immune cells: role in homeostasis and intestinal inflammation.* Inflamm Bowel Dis. 2010; 16: 1969-77.

http://dx.doi.org/10.1002/ibd.21304
PMid:20848507

61. von Andrian UH, Mackay CR. *T-cell function and migration. Two sides of the same coin.* N Engl J Med. 2000; 343: 1020-34.

http://dx.doi.org/10.1056/NEJM200010053431407
PMid:11018170

62. Stagg AJ, Kamm MA, Knight SC. *Intestinal dendritic cells increase T cell expression of alpha4beta7 integrin.* Eur J Immunol. 2002; 32: 1445-54.

http://dx.doi.org/10.1002/1521-4141(200205)32:5<1445::AID-IMMU1445>3.0.CO;2-E

63. Mora JR, Bono MR, Manjunath N, Weninger W, Cavanagh LL, Rosemblatt M et al. *Selective imprinting of gut-homing T cells by Peyer's patch dendritic cells.* Nature. 2003; 424: 88-93.

http://dx.doi.org/10.1038/nature01726
PMid:12840763

64. Johansson-Lindbom B, Svensson M, Wurbel MA, Malissen B, Márquez G, Agace W. *Selective generation of gut tropic T cells in gut-associated lymphoid tissue (GALT): requirement for GALT dendritic cells and adjuvant.* J Exp Med. 2003; 198: 963-9.

http://dx.doi.org/10.1084/jem.20031244
PMid:12963696 PMCid:PMC2194196

65. Mann ER, Bernardo D, Al-Hassi HO, English NR, Clark SK, McCarthy NE et al. *Human gut-specific homeostatic dendritic cells are generated from blood precursors by the gut microenvironment.* Inflamm Bowel Dis. 2012; 18: 1275-86.

http://dx.doi.org/10.1002/ibd.21893
PMid:21987473

66. Sigmundsdottir H, Pan J, Debes GF, Alt C, Habtezion A, Soler D et al. *DCs metabolize sunlight-induced vitamin D3 to 'program' T cell attraction to the epidermal chemokine CCL27.* Nat Immunol. 2007; 8: 285-93.

http://dx.doi.org/10.1038/ni1433
PMid:17259988

67. Iwata M, Hirakiyama A, Eshima Y, Kagechika H, Kato C, Song SY. *Retinoic acid imprints gut-homing specificity on T cells. Immunity.* 2004; 21: 527-38.

http://dx.doi.org/10.1016/j.immuni.2004.08.011
PMid:15485630

68. Bernardo D, Mann ER, Al-Hassi HO, English NR, Man R, Lee GH et al. *Lost therapeutic potential of monocyte-derived dendritic cells through lost tissue homing: stable restoration of gut specificity with retinoic acid.* Clin Exp Immunol. 2013; 174: 109-19.

http://dx.doi.org/10.1111/cei.12118
PMid:23607934 PMCid:PMC3784218

69. Johansson-Lindbom B, Svensson M, Pabst O, Palmqvist C, Marquez G, Förster R et al. *Functional specialization of gut CD103+ dendritic cells in the regulation of tissue-selective T cell homing.* J Exp Med. 2005; 202: 1063-73.

http://dx.doi.org/10.1084/jem.20051100
PMid:16216890 PMCid:PMC2213212

70. Coombes JL, Siddiqui KR, Arancibia-Cárcamo CV, Hall J, Sun CM, Belkaid Y et al. *A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism.* J Exp Med. 2007; 204: 1757-64.

http://dx.doi.org/10.1084/jem.20070590
PMid:17620361 PMCid:PMC2118683

71. Jaensson E, Uronen-Hansson H, Pabst O, Eksteen B, Tian J, Coombes JL et al. *Small intestinal CD103+ dendritic cells display unique functional properties that are conserved between mice and humans.* J Exp Med. 2008; 205: 2139-49.

http://dx.doi.org/10.1084/jem.20080414
PMid:18710932 PMCid:PMC2526207

72. Comino I, Al-Hassi HO, Suligoj T, Lee GH, Sousa C, Landy J et al. *Constitutive gut-homing capacity on circulating myeloid dendritic cells in coeliac disease.* Rev Esp Enferm Dig. 2014; 106: 64-65.

http://dx.doi.org/10.4321/S1130-01082014000100013
PMid:24689721

73. Milling S, Yrlid U, Cerovic V, MacPherson G. *Subsets of migrating intestinal dendritic cells.* Immunol Rev. 2010; 234: 259-67.

http://dx.doi.org/10.1111/j.0105-2896.2009.00866.x
PMid:20193024

74. Mowat AM. *Anatomical basis of tolerance and immunity to intestinal antigens.* Nat Rev Immunol. 2003; 3: 331-41.

http://dx.doi.org/10.1038/nri1057
PMid:12669023

75. Chirdo FG, Millington OR, Beacock-Sharp H, Mowat AM. *Immunomodulatory dendritic cells in intestinal lamina propria.* Eur J Immunol. 2005; 35: 1831-40.

http://dx.doi.org/10.1002/eji.200425882
PMid:16010704

76. Coombes JL, Maloy KJ. *Control of intestinal homeostasis by regulatory T cells and dendritic cells.* Semin Immunol. 2007; Apr;19(2):116-26.

http://dx.doi.org/10.1016/j.smim.2007.01.001

77. Hart AL, Al-Hassi HO, Rigby RJ, Bell SJ, Emmanuel AV, Knight SC et al. *Characteristics of intestinal dendritic cells in inflammatory bowel diseases.* Gastroenterology. 2005; 129: 50-65.

http://dx.doi.org/10.1053/j.gastro.2005.05.013
PMid:16012934

78. Bell SJ, Rigby R, English N, Mann SD, Knight SC, Kamm MA et al. *Migration and maturation of human colonic dendritic cells.* J Immunol. 2001; 166: 4958-67.

http://dx.doi.org/10.4049/jimmunol.166.8.4958
PMid:11290774

79. Steinman RM, Hawiger D, Liu K, Bonifaz L, Bonnyay D, Mahnke K et al. *Dendritic cell function in vivo during the steady state: A role in peripheral tolerance.* Ann N Y Acad Sci. 2003; 987: 15-25.

http://dx.doi.org/10.1111/j.1749-6632.2003.tb06029.x
PMid:12727620

80. Macpherson AJ, Uhr T. *Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria.* Science. 2004; 303(5664): 1662-5.

http://dx.doi.org/10.1126/science.1091334
PMid:15016999

81. Mora JR, Iwata M, Eksteen B, Song SY, Junt T, Senman B et al. *Generation of gut-homing IgA-secreting B cells by intestinal dendritic cells.* Science. 2006; 314: 1157-60.

http://dx.doi.org/10.1126/science.1132742
PMid:17110582

82. Benson MJ, Pino-Lagos K, Rosemblatt M, Noelle RJ. *All-trans retinoic acid mediates enhanced T reg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation.* J Exp Med. 2007; 204: 1765-74.

http://dx.doi.org/10.1084/jem.20070719
PMid:17620363 PMCid:PMC2118687

83. Sun CM, Hall JA, Blank RB, Bouladoux N, Oukka M, Mora JR et al. *Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid.* J Exp Med. 2007; 204: 1775-85.

http://dx.doi.org/10.1084/jem.20070602
PMid:17620362 PMCid:PMC2118682

84. Suzuki K, Maruya M, Kawamoto S, Sitnik K, Kitamura H, Agace WW et al. *The sensing of environmental stimuli by follicular dendritic cells promotes immunoglobulin A generation in the gut.* Immunity. 2010; 33: 71-83.

http://dx.doi.org/10.1016/j.immuni.2010.07.003
PMid:20643338

85. Strober W. *Vitamin A rewrites the ABCs of oral tolerance.* Mucosal Immunol. 2008; 1: 92-5.

http://dx.doi.org/10.1038/mi.2007.22
PMid:19079166

86. Denning TL, Wang YC, Patel SR, Williams IR, Pulendran B. *Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses.* Nat Immunol. 2007; 8: 1086-94.

http://dx.doi.org/10.1038/ni1511
PMid:17873879

87. Kang SG, Lim HW, Andrisani OM, Broxmeyer HE, Kim CH. *Vitamin A metabolites induce gut-homing FoxP3+ regulatory T cells.* J Immunol. 2007; 179: 3724-33.

http://dx.doi.org/10.4049/jimmunol.179.6.3724
PMid:17785809

88. Mora JR, Iwata M, von Andrian UH. *Vitamin effects on the immune system: vitamins A and D take centre stage.* Nat Rev Immunol. 2008; 8: 685-98.

http://dx.doi.org/10.1038/nri2378
PMid:19172691 PMCid:PMC2906676

89. Sigmundsdottir H, Butcher EC. *Environmental cues, dendritic cells and the programming of tissue-selective lymphocyte trafficking.* Nat Immunol. 2008; 9: 981-7.

http://dx.doi.org/10.1038/ni.f.208
PMid:18711435 PMCid:PMC3171274

90. Varol C, Vallon-Eberhard A, Elinav E, Aychek T, Shapira Y, Luche H et al. *Intestinal lamina propria dendritic cell subsets have different origin and functions.* Immunity. 2009; 31: 502-12.

http://dx.doi.org/10.1016/j.immuni.2009.06.025
PMid:19733097

91. Bogunovic M, Ginhoux F, Helft J, Shang L, Hashimoto D, Greter M et al. *Origin of the lamina propria dendritic cell network.* Immunity. 2009; 31: 513-25.

http://dx.doi.org/10.1016/j.immuni.2009.08.010
PMid:19733489 PMCid:PMC2778256

92. Schulz O, Jaensson E, Persson EK, Liu X, Worbs T, Agace WW et al. *Intestinal CD103+, but not CX3CR1+, antigen sampling cells migrate in lymph and serve classical dendritic cell functions.* J Exp Med. 2009; 206: 3101-14.

http://dx.doi.org/10.1084/jem.20091925
PMid:20008524 PMCid:PMC2806467

93. Mann ER, Landy JD, Bernardo D, Peake ST, Hart AL, Al-Hassi HO et al. *Intestinal dendritic cells: their role in intestinal inflammation, manipulation by the gut microbiota and differences between mice and men.* Immunol Lett. 2013; 150: 30-40.

http://dx.doi.org/10.1016/j.imlet.2013.01.007
PMid:23352670

94. Bain CC, Scott CL, Uronen-Hansson H, Gudjonsson S, Jansson O, Grip O et al. *Resident and pro-inflammatory macrophages in the colon represent alternative context-dependent fates of the same Ly6Chi monocyte precursors.* Mucosal Immunol. 2013; 6: 498-510.

http://dx.doi.org/10.1038/mi.2012.89
PMid:22990622 PMCid:PMC3629381

95. Nicoletti C, Arques JL, Bertelli E. *CX$_3$CR1 is critical for Salmonella-induced migration of dendritic cells into the intestinal lumen.* Gut Microbes. 2010; May-Jun;1(3):131-4.

http://dx.doi.org/10.4161/gmic.1.3.11711

PMid:21327020 PMCid:PMC3023593

96. Scott CL, Aumeunier AM, Mowat AM. *Intestinal CD103+ dendritic cells: master regulators of tolerance?* Trends Immunol. 2011; 32: 412-9.

http://dx.doi.org/10.1016/j.it.2011.06.003
PMid:21816673

97. Kinnebrew MA, Buffie CG, Diehl GE, Zenewicz LA, Leiner I, Hohl TM et al. *Interleukin 23 production by intestinal CD103(+)CD11b(+) dendritic cells in response to bacterial flagellin enhances mucosal innate immune defense.* Immunity. 2012; 36: 276-87.

http://dx.doi.org/10.1016/j.immuni.2011.12.011
PMid:22306017 PMCid:PMC3288454

98. Gibbons DL, Spencer J. *Mouse and human intestinal immunity: same ballpark, different players; different rules, same score.* Mucosal Immunol. 2011; 4: 148-57.

http://dx.doi.org/10.1038/mi.2010.85
PMid:21228770

99. Worthington JJ, Czajkowska BI, Melton AC, Travis MA. *Intestinal dendritic cells specialize to activate transforming growth factor-b and induce Foxp3+ regulatory T cells via integrin αvβ8.* Gastroenterology. 2011; 141: 1802-12.

http://dx.doi.org/10.1053/j.gastro.2011.06.057
PMid:21723222 PMCid:PMC3507624

100. Sanders TJ, McCarthy NE, Giles EM, Davidson KL, Haltalli ML, Hazell S et al. *Increased production of retinoic Acid by intestinal macrophages contributes to their inflammatory phenotype in patients with Crohn's disease.* Gastroenterology. 2014; 146: 1278-1288.

http://dx.doi.org/10.1053/j.gastro.2014.01.057
PMid:24503130

101. Cerovic V, Houston SA, Scott CL, *Aumeunier A, Yrlid U, Mowat AM, Milling SW. Intestinal CD103(-) dendritic cells migrate in lymph and prime effector T cells.* Mucosal Immunol. 2013; 6: 104-13.

http://dx.doi.org/10.1038/mi.2012.53
PMid:22718260

102. Denning TL, Norris BA, Medina-Contreras O, Manicassamy S, Geem D, Madan R et al. *Functional specializations of intestinal dendritic cell and macrophage subsets that control Th17 and regulatory T cell responses are dependent on the T cell/APC ratio, source of mouse strain, and regional localization.* J Immunol. 2011; 187: 733-47.

http://dx.doi.org/10.4049/jimmunol.1002701
PMid:21666057 PMCid:PMC3131424

103. Dudda JC, Lembo A, Bachtanian E, Huehn J, Siewert C, Hamann A et al. *Dendritic cells govern induction and reprogramming of polarized tissue-selective homing receptor patterns of T cells: important roles for soluble factors and tissue microenvironments.* Eur J Immunol. 2005; 35: 1056-65.

http://dx.doi.org/10.1002/eji.200425817
PMid:15739162

104. Edele F, Molenaar R, Gütle D, Dudda JC, Jakob T, Homey B et al. *Cutting edge: instructive role of peripheral tissue cells in the imprinting of T cell homing receptor patterns.* J Immunol. 2008; 181: 3745-9.

http://dx.doi.org/10.4049/jimmunol.181.6.3745
PMid:18768825

105. Rimoldi M, Chieppa M, Salucci V, Avogadri F, Sonzogni A, Sampietro GM et al. *Intestinal immune homeostasis is regulated by the crosstalk between epithelial cells and dendritic cells.* Nat Immunol. 2005; 6: 507-14.

http://dx.doi.org/10.1038/ni1192
PMid:15821737

106. Butler M, Ng CY, van Heel DA, Lombardi G, Lechler R, Playford RJ et al. *Modulation of dendritic cell phenotype and function in an in vitro model of the intestinal epithelium.* Eur J Immunol. 2006; 36: 864-74.

http://dx.doi.org/10.1002/eji.200535497
PMid:16544275

107. Iliev ID, Spadoni I, Mileti E, Matteoli G, Sonzogni A, Sampietro GM et al. *Human intestinal epithelial cells promote the differentiation of tolerogenic dendritic cells.* Gut. 2009A; 58: 1481-9.

108. Iliev ID, Mileti E, Matteoli G, Chieppa M, Rescigno M. *Intestinal epithelial cells promote colitis-protective regulatory T-cell differentiation through dendritic cell conditioning.* Mucosal Immunol. 2009B; 2: 340-50.

http://dx.doi.org/10.1038/mi.2009.13
PMid:19387433

109. Lee J, Mo JH, Katakura K, Alkalay I, Rucker AN, Liu YT et al. *Maintenance of colonic homeostasis by distinctive apical TLR9 signalling in intestinal epithelial cells.* Nat Cell Biol. 2006; 8: 1327-36.

http://dx.doi.org/10.1038/ncb1500
PMid:17128265

110. Lee J, Gonzales-Navajas JM, Raz E. *The "polarizing-tolerizing" mechanism of intestinal epithelium: its relevance to colonic homeostasis.* Semin Immunopathol. 2008; 30: 3-9.

http://dx.doi.org/10.1007/s00281-007-0099-7
PMid:18026955

111. Wells JM, Rossi O, Meijerink M, van Baarlen P. *Epithelial crosstalk at the microbiota-mucosal interface.* Proc Natl Acad Sci USA. 2011; 108. Suppl 1: 4607-14.

http://dx.doi.org/10.1038/embor.2012.96
PMid:22801555 PMCid:PMC3410395

112. Pott J, Hornef M. *Innate immune signalling at the intestinal epithelium in homeostasis and disease.* EMBO Rep. 2012; 13: 684-98.

http://dx.doi.org/10.1038/embor.2012.96
PMid:22801555 PMCid:PMC3410395

113. Fukata M, Breglio K, Chen A, Vamadevan AS, Goo T, Hsu D et al. *The myeloid differentiation factor 88 (MyD88) is required for CD4+ T cell effector function in a murine model of inflammatory bowel disease.* J Immunol. 2008; 180: 1886-94.

http://dx.doi.org/10.4049/jimmunol.180.3.1886
PMid:18209086 PMCid:PMC2828823

114. Szebeni B, Veres G, Dezsofi A, Rusai K, Vannay A, Bokodi G et al. *Increased mucosal expression of Toll-like receptor (TLR)2 and TLR4 in coeliac disease.* J Pediatr Gastroenterol Nutr. 2007; 45: 187-93.

http://dx.doi.org/10.1097/MPG.0b013e318064514a
PMid:17667714

115. Kalliomäki M, Satokari R, Lähteenoja H, Vähämiko S, Grönlund J, Routi T et al. *Expression of microbiota, Toll-like receptors, and their regulators in the small intestinal mucosa in celiac disease.* J Pediatr Gastroenterol Nutr. 2012; 54: 727-32.

http://dx.doi.org/10.1097/MPG.0b013e318241cfa8
PMid:22134550

116. Thomas KE, Sapone A, Fasano A, Vogel SN. *Gliadin stimulation of murine macrophage inflammatory gene expression and intestinal permeability are MyD88-dependent: role of the innate immune response in Celiac disease.* J Immunol. 2006; 176: 2512-21.

http://dx.doi.org/10.4049/jimmunol.176.4.2512
PMid:16456012

117. Palová-Jelínková L, Dáňová K, Drašarová H, Dvořák M, Funda DP, Fundová P et al. *Pepsin digest of wheat gliadin fraction increases production of IL-1β via TLR4/MyD88/TRIF/MAPK/NF-κB signaling pathway and an NLRP3 inflammasome activation.* PLoS One. 2013; 8: e62426.

http://dx.doi.org/10.1371/journal.pone.0062426
PMid:23658628 PMCid:PMC3639175

118. Maiuri L, Ciacci C, Ricciardelli I, Vacca L, Raia V, Auricchio S et al. *Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease.* Lancet. 2003; 362: 30-7.

http://dx.doi.org/10.1016/S0140-6736(03)13803-2

119. Di Sabatino A, Ciccocioppo R, Cupelli F, Cinque B, Millimaggi D, Clarkson MM et al. *Epithelium derived interleukin 15 regulates intraepithelial lymphocyte Th1 cytokine production, cytotoxicity, and survival in coeliac disease.* Gut. 2006; 55: 469-77.

http://dx.doi.org/10.1136/gut.2005.068684
PMid:16105889 PMCid:PMC1856172

120. Bernardo D, Garrote JA, Fernández-Salazar L, Riestra S, Arranz E. *Is gliadin really safe for non-coeliac individuals? Production of interleukin 15 in biopsy culture from non-coeliac individuals challenged with gliadin peptides.* Gut. 2007; 56: 889-90.

http://dx.doi.org/10.1136/gut.2006.118265
PMid:17519496 PMCid:PMC1954879

121. Matysiak-Budnik T, Candalh C, Dugave C, Namane A, Cellier C, Cerf-Bensussan N et al. *Alterations of the intestinal transport and processing of gliadin peptides in celiac disease.* Gastroenterology. 2003; 125: 696-707.

http://dx.doi.org/10.1016/S0016-5085(03)01049-7

122. Clemente MG, De Virgiliis S, Kang JS, Macatagney R, Musu MP, Di Pierro MR et al. *Early effects of gliadin on enterocyte intracellular signalling involved in intestinal barrier function.* Gut. 2003; 52: 218-23.

http://dx.doi.org/10.1136/gut.52.2.218
PMid:12524403 PMCid:PMC1774976

123. Maiuri L, Ciacci C, Auricchio S, Brown V, Quaratino S, Londei M. *Interleukin 15 mediates epithelial changes in celiac disease.* Gastroenterology. 2000; 119: 996-1006.

http://dx.doi.org/10.1053/gast.2000.18149
PMid:11040186

124. Meresse B, Chen Z, Ciszewski C, Tretiakova M, Bhagat G, Krausz TN et al. *Coordinated induction by IL15 of a TCR-independent NKG2D signaling pathway converts CTL into lymphokine-activated killer cells in celiac disease.* Immunity. 2004; 21: 357-66.

http://dx.doi.org/10.1016/j.immuni.2004.06.020
PMid:15357947

125. Hüe S, Mention JJ, Monteiro RC, Zhang S, Cellier C, Schmitz J et al. *A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease.* Immunity. 2004; 21: 367-77.

http://dx.doi.org/10.1016/j.immuni.2004.06.018
PMid:15357948

126. Ebert EC. *IL-15 converts human intestinal intraepithelial lymphocytes to CD94 producers of IFN-gamma and IL-10, the latter promoting Fas ligand-mediated cytotoxicity.* Immunology. 2005; 115: 118-26.

http://dx.doi.org/10.1111/j.1365-2567.2005.02132.x
PMid:15819704 PMCid:PMC1782126

127. DePaolo RW, Abadie V, Tang F, Fehlner-Peach H, Hall JA, Wang W et al. *Co-adjuvant effects of retinoic acid and IL-15 induce inflammatory immunity to dietary antigens.* Nature. 2011; 471: 220-4.

http://dx.doi.org/10.1038/nature09849
PMid:21307853 PMCid:PMC3076739