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Microreview

Dendritic cells in oral tolerance in the gut

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Summary

Oral tolerance is a process that allows generation of systemic unresponsiveness to food antigens. Hence if the same antigen is introduced systemically even under immunogenic conditions it does not induce immune responsiveness. Dendritic cells (DCs) have been identified as essential players in this process. DCs in the gut are located in a strategic position as they can interact directly with luminal antigens or indirectly after their transcytosis across epithelial cells. DCs can then migrate to associated lymphoid tissues to induce tolerance. Antigen presenting cells in the gut are specialized in function and have divided their labour so that there are cells capable to migrate to the draining mesenteric lymph node for induction of T regulatory cells, while other subsets are resident and are required to enforce tolerance locally in the gut after food antigen exposure. In this review, I shall summarize the characteristics of antigen presenting cells in the gut and their involvement in oral tolerance induction. In addition, I will also emphasize that tolerance to food allergens may be contributed by plasmacytoid DCs in the liver that participate to the elimination or anergy of allergen-specific CD8 T cells. Hence specialized functions are associated to different subsets of antigen presenting cells and different organs.

Introduction

Oral tolerance is the mechanism through which unresponsiveness to orally administered antigens is induced even if they are subsequently introduced systemically (Faria and Weiner, 2005). When this mechanism is defective, food allergies can arise (Brandtzaeg, 2010). As oral tolerance can induce unresponsiveness to the same antigens also to other districts, it could be exploited to desensitize against allergens that may enter via other sites (skin, airways, etc.). Hence, understanding the mechanisms responsible for oral tolerance induction can shed light on possible therapeutic intervention of food and other types of allergy (to airborne or skin antigens).

Dendritic cells (DCs) are professional antigen presenting cells (APCs) that are fundamental for the induction of immunity to a specific antigen (Ueno *et al.*, 2007). However, in addition to their well-characterized capacity to initiate immune responses, DCs are also potent inducers of tolerance and unresponsiveness to self and harmless foreign antigens (Steinman *et al.*, 2003; Rescigno, 2010a). Indeed, migratory mucosal DCs have been shown to be necessary for induction of tolerance towards orally administered antigens (Worbs *et al.*, 2006). Here I will first describe the characteristics of intestinal mucosa-associated DCs and then will review recent reports demonstrating the fundamental role of DCs in oral tolerance induction taking into account DCs both in the mesenteric lymph node and in the liver.

Gut mononuclear phagocytes

Antigen presenting cells with specialized functions have been described in the intestine. These cells are located in the lamina propria (LP) of the intestinal villi, in the mesenteric lymph nodes (MLN), in lymphoid aggregates and Peyer's patches (PP) (for extensive reviews see Rescigno and Di Sabatino, 2009; Pabst and Bernhardt, 2010; Rescigno, 2010b). Mesenteric lymphadenectomy abrogates oral tolerance induction indicating a crucial role of the MLN in this process (Worbs *et al.*, 2006). In addition, cellular transport of the antigen by $CCR7^+$ DCs is required for tolerance induction (Worbs *et al.*, 2006). Hence, it is likely that the main effectors of oral tolerance are LP-DC as this site is drained by the MLN and PP are not involved in oral tolerance (Spahn *et al.*, 2001). LP APCs can be classified into different subgroups depending on the expression of CX3CR1 (the receptor of fractalkine) and CD103 (αE integrin) (Denning *et al.*, 2007; Schulz *et al.*, 2009; Niess and Adler, 2010). However, as recently reported by Pabst (Pabst and Bernhardt, 2010) the LP of the small intestine is packed with cells with DC markers, but when these cells

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are isolated, their number is drastically reduced. This suggests either that we have not found the right conditions to purify the cells and we are missing a good proportion of them, or that we lose important cell surface markers during their isolation and this results in poor yields. In addition, the type and proportion of different subsets of DCs vary from laboratory to laboratory and whether the small or large intestines are considered. This suggests that different isolation procedures and/or the composition of the intestinal microbiota may contribute to increase variability on DC subtypes and function. Indeed, mice reared under germ-free conditions (i.e. in the absence of the intestinal microbiota) have different proportions of APC subsets (Niess and Adler, 2010). With this in mind, it is still possible to distinguish at least three types of APCs both in the small and in the large intestine: CX3CR1^{-}CD68^{-}CD103^{+} and CX3CR1intCD68^{-}CD103^{-} APCs and a population of classical macrophages CX3CR1^{+}CD68^{+}F4/80^{+}. For simplicity, from now on, the two major subsets of APCs will be named CD103^{+} and CX3CR1^{+} cells. Functionally, these phagocytes are very different, CD103^{+} DCs express indoleamine 2,3-dioxygenase (IDO) (Matteoli *et al*., 2010) and have been shown to drive T regulatory cell development via a TGF-β- and retinoic acid (RA)-dependent mechanism both in the mouse (Coombes *et al*., 2007; Sun *et al*., 2007) and in the human (Iliev *et al*., 2009b) system. CD103^{+} DCs can also imprint T cells with gut homing properties (Johansson-Lindbom *et al*., 2005; Jaensson *et al*., 2008). In contrast, CX3CR1^{+} cells can drive the development of Th17^{+} cells (Denning *et al*., 2007) presumably in response to microbial signals like Flagellin (Uematsu *et al*., 2008) or bacteria-released ATP (Atarashi *et al*., 2008). However, although CX3CR1^{+} cells share typical markers of DCs they have not been demonstrated to enter the lymphatics and to reach the draining lymph nodes (Schulz *et al*., 2009). As migration is a hallmark of DC function, it is not clear whether these cells can be considered as DCs and what is their potential to drive Th17 cells if they cannot reach the draining lymph node (Schulz *et al*., 2009). Hence hereafter CD103^{+} cells will still be considered as DCs while CX3CR1^{+} cells will be named mononuclear phagocytes. Indeed, even after *Salmonella* infection, the cell population that is found within the MLN carrying *Salmonella* is the CD103^{+} cells (Bogunovic *et al*., 2009). As mentioned above, the number and proportion of APC subsets depends on the microbiota, and in particular CX3CR1^{+} cells are drastically reduced in germ-free mice (Niess and Adler, 2010).

Origin of mononuclear phagocytes and environmental conditioning

The two phagocytic populations originate from different circulating precursors. CX3CR1^{+} cells derive from CX3CR1hi monocytes while CD103^{+} DCs derive from pre-DCs, in response to different growth factors (Bogunovic *et al*., 2009; Varol *et al*., 2009). CD103^{+} DCs are expanded by Flt3L while CX3CR1^{+} DCs are dependent on M-CSF (Bogunovic *et al*., 2009; Varol *et al*., 2009), further confirming their possible macrophage origin. It is likely that these cells acquire the typical mucosal functions once entering the LP as precursors. Indeed, CD103^{+} DCs that are tolerogenic in the gut are immunogenic in the skin, oral mucosa or the lungs (Bedoui *et al*., 2009; Ballesteros-Tato *et al*., 2010; Nudel *et al*., 2011). Hence, CD103 may be a tissue-acquired rather than a lineage marker. Consistently, blood pre-DCs that are the precursors of CD103^{+} DCs do not express markers of differentiated mucosal cells (Jaensson-Gyllenback *et al*., 2011). Our hypothesis is that CD103^{+} DCs acquire their mucosal phenotype in the LP. Indeed, we have shown that the simple incubation of bone marrow DCs with epithelial cell derived supernatant can induce the acquisition of the expression of CD103 and of RALDH2, the enzyme involved in vitamin A metabolism to RA. In addition, newly generated CD103^{+} DCs can drive Treg cell development that can protect against experimental colitis (Iliev *et al*., 2009a,b). We have also identified the factors released by epithelial cells that can drive CD103^{+} tolerogenic DCs. In the mouse, RA and TGF-β are both involved in tolerogenic DC differentiation (Iliev *et al*., 2009a) while in the human system also thymic stromal lymphopoietin (TSLP) is involved (Iliev *et al*., 2009b) presumably via the inhibition of the inflammatory potential of DCs (Rimoldi *et al*., 2005). Interestingly, LP-DCs are also characterized by the constitutive activity of β-catenin which is required for the production of RA, TGF-β and IL-10 by DCs (Manicassamy *et al*., 2010), hence it would be interesting to know whether epithelial cells can activate the WNT signalling pathway that leads to β-catenin activation in DCs. It is important to note that epithelial cells may not be the only cells capable of conditioning non-inflammatory DCs. Indeed, several of these immunomodulatory factors are produced also by other sources. For instance, RA is produced by stromal cells (Molenaar *et al*., 2009) and by the liver and released in the duodenum via the bile (Jaensson-Gyllenback *et al*., 2011). RA can induce the expression of retinal dehydrogenase (RALDH2) in DCs that also acquire the ability to convert retinal into RA (Iliev *et al*., 2009a; Jaensson-Gyllenback *et al*., 2011; Molenaar *et al*., 2011). Although other factors may result in increased RALDH expression in DCs like GM-CSF and IL4 (Yokota *et al*., 2009), in mice under long-term vitamin A deficiency, CD103^{+} DCs lack the expression of RALDH (Jaensson-Gyllenback *et al*., 2011; Molenaar *et al*., 2011). This suggests that at least in the gut, RA may be the most important inducer of RALDH in DCs. In addition retinol is found in different concentrations across the gut (more in the small than the large intestine) and this correlates with the expres-

sion of RALDH2 in CD103$^+$ DCs as for instance cells isolated from the small intestine and not from the colon express RALDH2 (Jaensson-Gyllenback *et al*., 2011). In the mesenteric lymph nodes stromal cells have also been shown to express RA and may contribute to preserve RALDH expression by DCs at this site and to imprint gut homing properties to T cells (Hammerschmidt, 2008). Also other factors may be involved in controlling the generation of tolerogenic DCs, these include IL-10 and prostaglandin (PG)-E2 (Newberry *et al*., 1999; 2001), but their exact role in conditioning mucosal DCs remains to be established. This is particularly true in light of a recent publication showing that PGE-2 is a negative regulator of RALDH2 expression and thus it reduces the capacity of DCs to produce RA (Stock *et al*., 2011). As PGE-2 is abundantly expressed in the gut (Newberry *et al*., 2001), it would be interesting to know why gut CD103$^+$ DCs still express RALDH2.

Same cell type, different function

CD103$^+$ cells are not always tolerogenic and can become inflammatory under intestinal inflammation as they lose the ability to drive Foxp3$^+$ Tregs but drive IFN-γ^+ cells (Laffont *et al*., 2010). It is not clear whether these inflammatory CD103$^+$ cells are coming from the LP where they change their properties during inflammation or whether they are recruited as progenitors and fail to become tolerogenic under the inflammatory microenvironment, or alternatively whether they are recruited directly to the MLN during inflammation and hence have not been conditioned by the gut microenvironment. This adjustment to the local microenvironment may allow the establishment of immunity.

On the other hand also CX3CR1$^+$ phagocytes are not always pro-inflammatory. Even though these cells can support Th17 cell differentiation (Denning *et al*., 2007; Atarashi *et al*., 2008; Uematsu *et al*., 2008), and can participate to worsen intestinal inflammation (Fortin *et al*., 2009; Varol *et al*., 2009; Niess and Adler, 2010), they have been shown to release IL-10 in a CX3CL1-dependent way and to support the expansion of Treg cells during oral tolerance (Hadis *et al*., 2011). It is not clear whether the differences of function (inflammatory versus tolerogenic) in both phagocytes are associated to the microenvironment found in the gut when they arrive as monocyte precursors that determines their differentiation into inflammatory or tolerogenic cells.

Requirements of mucosal DCs to drive oral tolerance to proteins

It has been shown that DCs are involved in oral tolerance induction in the MLN (Worbs *et al*., 2006). Given the important role of CD103$^+$ DCs to drive the development of Foxp3$^+$ Tregs via RA and TGF-β (Coombes *et al*., 2007; Sun *et al*., 2007; Iliev *et al*., 2009a), it is possible that this subset is involved in oral tolerance induction. However, several other factors have been shown to participate to oral tolerance induction. IDO is an enzyme involved in tryptophan catabolism. Its immunosuppressive effects are linked to the reduction of local tryptophan concentration that has detrimental effects on T cell proliferation, and to the production of immunomodulatory tryptophan metabolites (Munn and Mellor, 2007) that contribute to the activation or *de novo* induction of Tregs (Fallarino *et al*., 2006; Sharma *et al*., 2007). We found that CD103$^+$ DCs selectively express IDO that is involved in reducing the proliferation of T cells and fostering their differentiation into Foxp3$^+$ Tregs (Matteoli *et al*., 2010). In addition IDO inhibition *in vivo* abrogates the development of oral tolerance (Matteoli *et al*., 2010). IDO may facilitate the RA-dependent TGF-β activity on Foxp3 upregulation (Chen *et al*., 2003; Shevach *et al*., 2008; Xiao *et al*., 2008), alternatively, and non-mutually exclusive, TGF-β may be required to sustain IDO expression (Belladonna *et al*., 2008). As TGF-β is abundantly expressed in the gut and is also released by mucosal DCs (Iliev *et al*., 2009a), it is possible that it might be involved in upregulating IDO expression. Alternatively, in human DCs, PG-E2 has been shown to upregulate the expression of IDO (Braun *et al*., 2005), but, as mentioned earlier PGE-2 has a negative role in RALDH2 expression (Stock *et al*., 2011) and hence it may have an opposite role.

IDO is not the only mediator of oral tolerance. Other factors have been shown to participate. These include membrane-bound co-stimulatory molecules of the B7-CD28 family like B7-H1 (PD-L1, CD274) and B7-DC (PD-L2) (Fukaya *et al*., 2010). MLN DCs lacking these molecules are impaired in driving Foxp3$^+$ Tregs. It is not clear though whether these molecules are preferentially expressed in the CD103$^+$ subset of MLN DCs. It is likely that this is the case as these cells are particularly apt at driving Treg differentiation. Interestingly, similar to IDO KO DCs, B7-H1 or B7-DC KO DCs are more prone to drive Th17 T cells, indicating that when Treg differentiation is inhibited, Th17 T cell differentiation is fostered (Fukaya *et al*., 2010; Matteoli *et al*., 2010).

Another mechanism to drive oral tolerance by gut DCs is via specific targeting of the C-type lectin SIGNR1 (Zhou *et al*., 2010). This lectin is preferentially expressed on the CD11c$^+$CD11b$^+$ LP-DC subtype which partly express CD103. Interestingly though, tolerance to mannosylated proteins that bind SIGNR1 results in the generation of IFN-γ/IL-10 double producer T cells that share features with T regulatory cells of the Tr1 type rather than Foxp3$^+$ Tregs (Zhou *et al*., 2010). This indicates that the nature of the antigen may lead to different types of regulatory T cells.

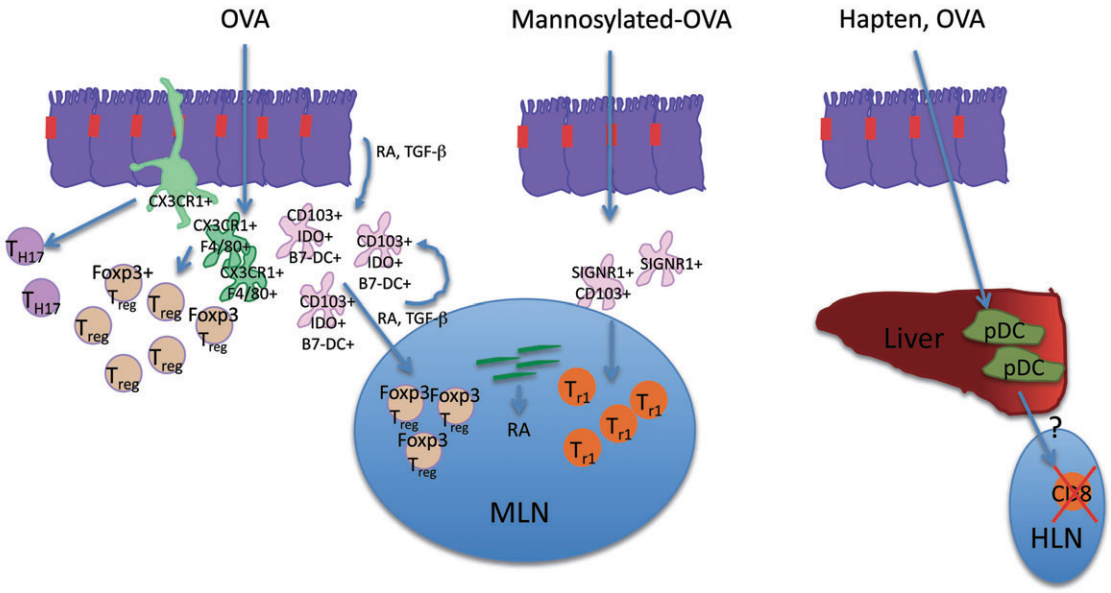

Fig. 1. Oral tolerance induction is a complex event involving different routes, cell types and organs.
Left: Soluble proteins are taken up by cd103$^+$IDO$^+$ DCs that migrate to the draining MLN and induce the differentiation of Foxp3$^+$ Tregs via a TGF-β- and RA-dependent mechanism. DC-produced RA can act on DCs to induce RALDH expression in an autocrine fashion. In the MLN also stromal cells produce RA and this may contribute to maintain RALDH expression in DCs. CD103$^+$ DCs likely express also B7H1$^+$B7-DC$^+$, but this needs to be proven. Activated Tregs are then restimulated in the LP by CX3CR1$^+$F4/80$^+$ macrophages. CX3CR1$^+$ cells have been described also to drive Th17 T cell differentiation *in vitro*.
Middle: Highly mannosylated proteins are targeted to SIGNR1$^+$CD103$^+$ DCs that can induce the differentiation of IFN-γ$^+$IL-10$^+$ Tr1 T regulatory cells.
Right: Soluble proteins and haptens can reach the liver via the portal vein. Liver pDCs take up the haptens and is not clear whether they migrate to the hepatic lymph node or whether they remain in the liver to anergize or delete hapten-specific CD8 T cells.

Hence oral tolerance to proteins can be mediated by Foxp3$^+$ Tregs or by Tr1, depending on the nature of the protein (mannosylated and non-mannosylated).

Balance among molecules

As mentioned above, when IDO is knocked out in DCs, these cells lose the ability to drive Tregs and foster the development of Th17 cells, and the same is true when B7-DC is knocked out. This is not entirely surprising as the generation of Tregs depends on TGF-β but, in the presence of IL-6, Th17 development is favoured (Bettelli *et al.*, 2006). Similarly, RA that is required together with TGF-β to foster Treg development, when in conjunction with IL-15 it can completely block TGF-β induced Treg differentiation and foster Th1 polarization (DePaolo *et al.*, 2011). This has detrimental effects in tolerance induction to dietary antigens, like gliadin, and can rather drive pathologic inflammation that can lead to coeliac disease-like syndrome in mice humanized for HLA-DQ8 expression (DePaolo *et al.*, 2011). Hence the balance between factors involved in tolerance or immunity is very subtle.

DCs in oral tolerance in the liver

The role of the liver in oral tolerance induction has been thoroughly demonstrated, including using transplant of liver from mice orally fed with a model antigen (Li *et al.*, 2004). However, the involvement of DCs in this process and the mechanism of tolerance was not addressed. A recent report has proposed a role for liver plasmacytoid (p)DCs in oral tolerance (Goubier *et al.*, 2008). Differently from conventional DCs, pDCs are characterized by their lymphoid origin (Cisse *et al.*, 2008). Depletion of pDCs *in vivo* abrogated oral tolerance induction to a hapten and reduced by 50% systemic tolerance to a soluble model antigen (Goubier *et al.*, 2008). However, as pDC depletion was systemic, it cannot be excluded a role of these cells at other organs than the liver. The mechanism of oral tolerance in this system is not dependent on the induction of Tregs, but rather to anergy or depletion of antigen-specific CD8 T cells (Goubier *et al.*, 2008), indicating that pDCs are mainly involved in the elimination of antigen-specific cytotoxic T cells via a mechanism that is independent of CD4$^+$T cells.

Conclusions

In conclusion, all of the APC subsets present in the LP can participate to oral tolerance induction (Fig. 1). CD103$^+$ DCs are able to migrate to the mesenteric lymph node and initiate tolerance via the induction of Foxp3$^+$ Tregs. This is achieved through the expression of IDO that

catabolizes tryptophan and reduces its local concentration thus affecting T cell proliferation and leads to the production of immunomodulatory metabolites involved in Treg differentiation; the release of TGF-β and RA that are likely involved in inducing Foxp3 upregulation and the expression of B7-H1 and B7-DC co-stimulatory molecules. SIGNR1$^+$CD11c$^+$CD11b$^+$ DCs that partly express CD103 can induce Tr1 cells that produce IL-10 and IFN-γ in response to highly mannosylated proteins. CX3CR1$^+$ APCs express IL-10 in response to CX3CL1 and restimulate Tregs specific for fed antigens *in situ*. This enforces establishment of tolerance to food antigens. Tolerance can be achieved also at the CD8 T cell level after transfer of fed antigens to the liver via the action of pDCs that induce anergy or deletion of antigen-specific CD8 T cells. Hence CD8 tolerance is achieved by pDCs while CD4 tolerance is achieved in the MLN by LP-DCs.

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