INTESTINAL DENDRITIC CELL AND MACROPHAGE SUBSETS: TIPPING THE BALANCE TO CROHN'S DISEASE?

M. K. Magnusson and M. J. Wick*

Department of Microbiology and Immunology, University of Gothenburg,
Gothenburg, Sweden

Dendritic cells and macrophages play an essential role in immune homeostasis in the intestine. They have the critical task of maintaining the balance between tolerance to the intestinal microflora and potential food antigens while retaining the ability to initiate immunity against pathogens. For patients with Crohn's Disease, the tolerance/immunity balance is disturbed and these individuals suffer from chronic intestinal inflammation driven by aberrant T cell reactivity to intestinal bacteria. As antigen presenting cells are required for T cell activation, intestinal phagocytes with the capacity to present antigens from intestinal bacteria to T cells are likely involved in initiating and propagating Crohn's Disease. Recent data describe unique subsets of human intestinal phagocytes that may be involved in the aberrant reactivity to commensal flora that drives Crohn's Disease pathogenesis. This review summarizes the current knowledge of phagocyte subsets in the intestine and mesenteric lymph nodes in healthy individuals and Crohn's Disease patients. Deciphering the function of intestinal phagocytes in health and disease is crucial to advance our understanding of the cellular mechanisms underlying this debilitating disease, provides a potential way to improve treatment for patients with inflammatory bowel disease.

Keywords: Crohn's Disease, dendritic cell, macrophage, intestine, commensal bacteria

Introduction

Crohn's Disease is an enigmatic inflammatory disorder of the gut whose prevalence varies in different populations and geographic locations [1]. It is a chronic, recurrent disorder that causes major disability, suffering and occasionally death due to complications. The onset of Crohn's Disease is typically at 15–30 years of age and thus the patient group is often quite young. The disease is characterized by transmural intestinal inflammation that most frequently occurs in the distal ileum. Another relatively common location is the colon, where one frequently sees segmental disease. The inflammation can lead to serious complications including bowel obstruction, fistulae and abscesses. Patients also have an increased risk for colorectal cancer, with the duration and extent of the inflammatory disease being risk factors [2].

The environment where Crohn's Disease occurs is unique. That is, the intestine has the critical task of allowing us to respond to eventual infections yet must tolerate our intestinal bacteria and potential food antigens. Maintaining the balance between tolerance and immunity is not necessarily easy, and when the balance is tipped from the normal, desired state of tolerance to unwanted chronic inflammation, the results are severe. Why the balance gets tipped towards undesired chronic inflammation and how it can be effectively treated are poorly understood.

Overreactivity to intestinal bacteria underlies Crohn's Disease

Current hypotheses suggest that Crohn's Disease patients have an aberrant immune response to normal intestinal bacteria [3, 4] and, for unknown reasons, react inappropriately and develop chronic intestinal inflammation. In support of this, it has been shown that antibiotics dampen the symptoms of Crohn's patients and the effect is reversed when treatment is terminated [5]. Also, clinical experiments in patients with active colonic disease where the fecal stream was diverted by a proximal ileostomy led to resolution of the inflammation, but the patients suffered a relapse when the bowel luminal contents were re-introduced [6, 7]. In addition, it has been shown that Crohn's patients have a defect in bacterial clearance [8] and polymorphisms in receptors that recognize bacteria are overrepresented in patients [3, 4]. The microflora in the intestinal mucosa and fecal samples from Crohn's patients has also shown significant changes compared to controls, often with a predominance of potentially harmful bacteria or a decrease in beneficial bacteria [9, 10]. Finally, studies in animal models show that bacteria are required to develop chronic intestinal inflammation and aberrant bacterial recognition can trigger the breakdown of intestinal tolerance [3–5]. Thus, bacteria are important in intestinal inflammation, although the mechanism is poorly understood. The general picture is that an aggressive T cell immune response to commensal bacteria occurs in geneti-

*Corresponding author: Mary Jo Wick; Dept. Microbiology and Immunology, University of Gothenburg, Box 435 405 30 Gothenburg, Sweden; Phone: +46 31 786 6325; E-mail: mary-jo.wick@immuno.gu.se

cally susceptible persons where undefined environmental factors precipitate the disease. Crohn's Disease patients differ from healthy persons, who remain "tolerant" to their intestinal bacteria and do not start an inflammatory response.

What immune mechanisms perpetuate the inflammation in Crohn's Disease patients?

As outlined above, patients seem to have aberrant reactions to intestinal bacteria. But how does this perpetuate the inflammation? The pathology is caused by cytokine-producing CD4⁺ T lymphocytes that recognize commensal bacteria [5, 11]. The link between bacteria and activation of pathologic T lymphocytes occurs through Dendritic cells (DCs). DCs are abundant in the intestine and can take up bacteria [12, 13]. The DC then breaks down the bacteria into peptides, which are "presented" to T lymphocytes. T lymphocytes get activated, proliferate and initiate an immune response, which in the case of Crohn's Disease is harmful. Despite their ability to activate T lymphocytes, DCs are, ironically, also crucial for keeping tolerance to intestinal bacteria and food [13, 14]. Most people do not develop intestinal inflammation because DCs maintain "tolerance" to their commensal bacteria and food. Thus, DCs are critical cells regulating the balance between tolerance to food and commensal bacteria while keeping the possibility to start immunity to pathogens [13, 14].

Two main factors are central to directing the tolerance/immunity balance. One is the environment. In particular, the intestine has unique properties that "instruct" DCs, as well as macrophages, to maintain tolerance unless strong signals of infection arise [13–16]. The second factor relates to distinct types of DCs in the intestine that seem to have distinct physiological activities [13, 14]. For example, different DC subpopulations in the intestinal lamina propria of mice have been characterized. In particular, tissue resident CD11c^{hi/lo}CD11b^{hi}CX3CR1⁺ cells and migratory CD11c^{hi}CD11b^{hi/lo}CD103⁺ DCs have been described in detail [14, 17, 18]. It has been shown that resident CX3CR1⁺ cells sample antigens from the intestinal lumen, are poor at priming naïve T-cells and are phenotypically indistinguishable from tissue resident macrophages [19]. In contrast, migratory CD103⁺ DCs move from the intestine after they have taken up antigen to the draining lymph node where they initiate adaptive immune responses [18–20]. T lymphocytes then migrate to the intestine and can either actively maintain tolerance by producing anti-inflammatory factors, such as IL-10 and TGF- β , or cause pathology [21]. In contrast, DCs not expressing CD103 are not migratory and instead promote intestinal inflammation when conditions permit [19, 22–24].

Intestinal subsets of both DCs and macrophages in mice are well described but little is known about the situation in humans. Most studies on human DCs, both in Crohn's Disease and healthy subjects, have been performed using blood-derived cells. However, DCs derived from cultured blood cells differ from cells isolated directly from tissue. Importantly, results may even be misleading since DC function is

tightly regulated by the local microenvironment, particularly in the intestine [13, 14, 16]. Another cell type that makes the picture of intestinal inflammation even more complex is monocytes/macrophages. These cells promote inflammation and can thus also influence the inflammatory status [8, 15, 25, 26]. Indeed, very little is known about the phenotype and function of human intestinal DCs and macrophages, particularly from patients with intestinal inflammatory disorders.

Phagocyte subsets in the human intestine

As in mice, the lamina propria of the colon and ileum in humans is populated by different subsets of DCs and macrophages with potential pro- or anti-inflammatory properties. However, unlike the situation in mice, relatively few studies have been performed on phagocyte subsets from human intestinal tissues. This is likely due to difficulties in obtaining large enough samples from the relevant tissues to identify these scarce cells. However, studies using immunohistochemistry have been performed on biopsies from the colon of normal individuals and Crohn's Disease patients and showed the presence of different subsets of phagocytes in human colon [27–30]. Information obtained from immunohistochemical stainings is invaluable since they also show the location of the cells within the tissue. Nevertheless, characterizing cells in a more detailed fashion requires simultaneous staining using antibodies against several surface and intracellular molecules. This is greatly facilitated using multicolor flow cytometry. A difficulty, however, is that there is no uniform way of looking at different phagocyte subtypes in human intestine. Presently, a large number of distinct markers and functions are used, which complicates direct comparison of data obtained in different studies. Also, there is an overlap between different DC and macrophage subsets, which emphasizes the plasticity and complexity of the myeloid cell lineage. This is exemplified in the study by Verstege et al. [30] who demonstrated that human intestinal DCs are a heterogeneous family of cells with different functions that lack a distinct marker allowing their identification.

For identification of DCs and DC subsets, most gating strategies have made use of the HLADR⁺CD11c⁺ fraction of lin⁻ cells. From this population, different subsets can be identified using a variety of surface markers. Gating strategies for macrophages have been less uniform but commonly make use of the macrophage markers CD33 and/or CD14. Previously, it was shown that CD14 expression was down regulated on intestinal macrophages [31]. However, several studies have now confirmed expression of CD14 on these cells [32, 33]. *Table 1* lists the characteristics of the different intestinal phagocyte subsets described in this review.

CD1c (BDCA-1) is a widely used marker for myeloid DCs in peripheral blood and has also been used successfully to identify intestinal phagocytes. One DC subset that has been identified by CD1c in the colon and jejunum is myeloid HLADR⁺CD19⁻CD1c⁺ DCs [34]. These cells were shown to have a more activated phenotype (CD40⁺,

Table 1. Phenotypic description of phagocyte subsets in human intestine*

Phenotype	Other surface molecules	Comment	References
HLADR ⁺ CD19 ⁻ CD1c ⁺ CD303 ⁻	CD40 ⁺ CD86 ⁺ CD83 ⁺ CCR7 ⁺	DC subset Co-expression of CD103 on <5% of the cells	[34]
CD14 ⁻ CD19 ⁻ CD11c ⁺ CD1c ⁺		DC subset	[35]
HLADR ⁺ CD11c ⁺ CD103 ⁺ CD1c ⁺ CD163 ⁻		DC subset	[37]
HLADR ⁺ CD11c ⁺ CD103 ⁺ CD1c ⁻ CD163 ⁻		DC subset	[37]
HLADR ⁺ CD11c ⁺ CD103 ⁻ CD1c ⁺ CD163 ⁻		DC subset	[37]
HLADR ⁺ CD11c ⁺ CD103 ⁻ CD1c ⁻ CD163 ⁺	CD14 ⁺	Macrophage subset	[37]
HLADR ⁺⁺ CD14 ⁺ CD33 ⁺	CD205 ⁺ CD209 ⁺	Macrophage subset	[32]
HLADR ⁺ CD14 ⁻ CD33 ⁺		Macrophage subset	[32]
BDCA-2 ⁺		Plasmacytoid DCs	[30]

*Subsets may be overlapping or even describe the same populations but are added to the table as different entities.

CD86⁺, CD83⁺) and express CCR7 in contrast to their counterparts in peripheral blood [34]. Co-expression of CD103 was found on approximately 4% of the cells. A similar population was identified by Baumgart et al. [35] as being CD14⁻CD19⁻CD11c⁺CD1c⁺. It is difficult to know if these cells correspond to migratory or tissue resident phagocytes since they express the migratory molecule CCR7 but few express CD103. However, it is important to remember that the data concerning migratory CD103⁺ cells have been derived in mice and we do not know about the situation in humans. However, it has been shown that CD103⁺CD11c⁺HLADR⁺ cells derived from human colon express Indoleamine 2,3-dioxygenase, which in mice is involved in the ability of CD103⁺ DCs to drive Foxp3⁺ Treg cell development [36]. This suggests similarity between CD103⁺ DCs in mice and humans.

The existence of CD1c⁺ and CD103⁺ DC subsets has also been studied in duodenal mucosa in patients with celiac disease and healthy controls. A recent study identified a HLADQ⁺HLADR⁺CD11c⁺ DC population where approximately 50% of the cells expressed CD103 [37]. In this study they also found that ~60% of these cells expressed CD1c and there was a 20–50% overlap in the CD103 and CD1c populations. The HLADQ⁺HLADR⁺CD11c⁺ population could be divided into four distinct subsets: CD103⁺CD1c⁺CD163⁻, CD103⁺CD1c⁻CD163⁻, CD103⁻CD1c⁺CD163⁻ and CD103⁻CD1c⁻CD163⁺ (Table 1). CD163 is a typical macrophage marker and approx. 90% of the CD163⁺ cells co-expressed CD14, identifying these cells as monocyte-derived macrophages. CD14 was absent on the other subsets, which may suggest that they originate from other precursor cells. In mice it has been shown that myeloid DCs originate from pre-DCs [19]. Despite recent progression defining DC subsets in the human intestine based on phenotype, nothing is yet known about their function in health and disease.

For myeloid DC subsets, the most common and thus far most relevant markers have been HLADR, CD11c, CD1c and CD103. New markers, however, will most likely ap-

pear. One such marker may be BDCA3, which was recently identified to be expressed on a population of lin⁻HLADR⁺ cells in human blood. These cells were shown to efficiently cross present exogenous antigens, induce a Th1 response and express DNGR-1 (CLEC9A) [38–41]. They have been suggested to be homologous to mouse CD8 α DCs. In intestinal tissues, it has been shown that BDCA3⁺ cells are absent in human duodenal mucosa [42]. However, they are abundant in human colon and MLNs [30]. Plasmacytoid DCs are beyond the scope of this review but, in general, markers for these cells are BDCA-2 (CD303) and CD123 [43]. Plasmacytoid DCs have been found in lymph follicles in human colon but are absent in the mucosa [30].

Other important phagocytes are, of course, macrophages. Similar to intestinal DCs, macrophages are likely composed of several subsets in the human lamina propria. As mentioned above, CD33, CD14 and CD163 are typical macrophage markers which, in addition to CD68, have been used as pan-macrophage markers. Recently, extensive characterization of CD14⁺CD33⁺ and CD14⁻CD33⁺ macrophages from human colonic mucosa was performed where the CD14⁺CD33⁺ fraction also expressed typical DC markers (CD205 and CD209) and produced larger amounts of pro-inflammatory cytokines (IL-23, TNF- α and IL-6) [32]. Interestingly, these cells also expressed CX3CR1, a marker of tissue resident myeloid cells in mice. In another report from the same group, it was shown that the CD14⁺CD209⁺ macrophages induced proliferation of naïve CD4⁺ T cells as well as monocyte-derived DCs [33]. The authors speculate that these cells are not precursors for DCs but possess some DC-like Ag presenting features, again underlining the complexity of the myeloid system.

DC subsets in human mesenteric lymph nodes

Migratory DCs sample antigens from the intestine and travel to the mesenteric lymph nodes (MLNs) draining the colon

and ileum to present internalized antigen to naïve CD4⁺ T cells. In mice, it has been shown that the DCs involved in this action express CD103, promote induction of CD4⁺ T regulatory cells (T_{regs}) and induce the gut-tropic receptors CCR9 and $\alpha 4\beta 7$ on CD4⁺ T cells [20, 21, 44]. As many as 40% of the cells in MLNs express CD103. These cells also express CD40 and CCR7, suggesting that they are activated and derived from the gut [20]. Different DC subsets in human MLNs have recently been described and are summarized in Table 2. In two different studies, the presence of CD103⁺ and CD103⁻ DC subsets in MLNs has been reported [20, 45]. The CD103⁺ population had a higher expression of CD40, CD83 and CCR7 compared to the CD103⁻ population and probably represents an activated lamina propria-derived migratory DC population [45]. In addition, allogeneic mixed lymphocyte reactions between CD103⁺ DCs and naïve CD4⁺ T cells induced FoxP3⁺ T_{reg} cells with a reduction of IFN- γ production [45] as well as induced expression of the gut homing receptors CCR9 and $\alpha 4\beta 7$ on the CD4⁺ T cells [20]. This is consistent with studies in mice.

In addition to studies examining CD103⁺ cells, a study of human MLN DCs identified three different subsets: myeloid DCs (CD11c⁺CD123⁻HLADR⁺), plasmacytoid DCs (CD11c⁻CD123⁺HLADR⁺) and mature DCs (CD11c⁺CD123⁺HLADR⁺⁺) [46]. However, the relationship of these subsets to the CD103⁺ DCs described above is not known. Nevertheless, the mature DCs expressed higher levels of CD40, CD86 and CD83 and induced low levels of IFN- γ in an allogeneic MLR [46], which resembles the results from migratory CD103⁺ cells.

Phagocyte subsets in the intestine of patients with Crohn's Disease

Crohn's Disease is characterized by sustained activation of increased numbers of immune cells in the intestinal mucosa. In particular, lymphocytes producing inflammatory

cytokines such as TNF- α , IFN- γ , IL-17 and IL-1 β are associated with disease [5, 47]. The local release of cytokines and other inflammatory mediators likely increases recruitment and activation of more immune cells to perpetuate the inflammation. In addition, the cytokine environment of the intestine can influence the differentiation of T cells, which in turn influences the balance between inflammation and tolerance. Crohn's Disease has been suggested to be a primary immunodeficiency of macrophages (reviewed in [48] and [49]). Whether this holds true, or if there is a functional disorder in a specific phagocyte subset or in the microenvironment that influences particular subset(s), remains to be shown. Indeed, causes underlying this disease are likely multifactorial. In general, studies have shown an increase in both DC and macrophage populations in the intestinal lamina propria in Crohn's Disease patients [20, 32, 33, 50–52]. Studies have also consistently shown that DCs in Crohn's Disease are more activated and have higher expression of microbial recognition receptors, particularly TLR4 [8, 27, 50, 53, 54]. These findings support intestinal phagocytes as likely key mediators of the pro-inflammatory response.

Similar conclusions have been drawn from studies on cytokine profiles, as Crohn's Disease is associated with a Th1/Th17 immune response and an imbalance of pro- and anti-inflammatory cytokines [55]. Since essential cytokines for Th1 and Th17 development are produced by antigen presenting cells, these cells may be the primary mediators of the secondary pro-inflammatory T-cell infiltration seen in Crohn's Disease. Thus far there are very few studies examining cytokine expression from intestinal phagocytes, and no studies have examined cytokine expression by phagocyte subsets. However, it has been shown that IL-6 and IL-12 are over-produced by DCs from Crohn's Disease patients [53]. Consistent with this, Ng et al. [54] showed that DCs from patients with Crohn's Disease express more IL-12p40 and IL6 compared to healthy controls. Finally, LPS stimulation of mucosal DCs in Crohn's Disease patients induced high secretion of TNF α and IL-8 [35].

Table 2. Phenotypic description of DC subsets in human MLN*

Phenotype	Other surface molecules	Comment	References
HLADR ⁺ CD11c ⁺ CD103 ⁺	CCR7 ⁺ CD40 ⁺⁺ CD83 ⁺⁺	Migratory DCs derived from the gut?	[20, 45]
HLADR ⁺ CD11c ⁺ CD103 ⁻	CCR7 ⁻ CD40 ^{lo} CD83 ^{lo}		[20, 45]
HLADR ⁺ CD11c ⁺ CD123 ⁻	CD40 ⁺ CD80 ⁺⁺ CD86 ⁺	Termed myeloid DCs.	[46]
HLADR ⁺⁺ CD11c ⁺ CD123 ⁺	CD40 ⁺⁺ CD80 ⁺ CD86 ⁺⁺ CD83 ⁺	Termed mature DCs.	[46]
HLADR ⁺ CD11c ⁻ CD123 ⁺	CD86 ⁺	Plasmacytoid DCs.	[46]

*Subsets may be overlapping or even describe the same populations but are added to the table as different entities.

For macrophages, it has been shown that CD14⁺ intestinal macrophages from patients with Crohn's Disease produced abundant IL-23 and TNF- α in response to stimulation with commensal bacteria [32]. This induced an IL-23/IFN- γ positive feedback loop contributing to the intestinal inflammation [32]. The same group also reported expression of robust amounts of IL-6, IL-1 β and IL-23 in MLR supernatants from co-cultures of CD4⁺ T cells with LP CD14⁺ macrophages [33]. Taken together, observations from several groups suggest the role of phagocytes as mediators of a skewed Th1/Th17 response in Crohn's Disease.

DC subsets in mesenteric lymph nodes of patients with Crohn's Disease

Very few studies have been performed on MLNs from patients with Crohn's Disease. So far it has been shown that there are increased numbers of CD103⁺ DCs in MLNs from Crohn's Disease patients, and these cells are able to stimulate CCR9 and α 4 β 7 expression on CD8⁺ T cells similar to their counterparts from healthy controls [20]. Thus, it seems gut homing properties should be intact. It has also been shown that myeloid DCs (CD11c⁺CD123⁺HLADR⁺) from MLNs of Crohn's Disease patients secrete high amounts of IL-23 and low amounts of IL-10 that promote IFN- γ production by CD4⁺ T cells [46]. This resulted in a Th1/Th17 unbalance and may indicate that MLNs are a site of disease induction [46]. An important unaddressed issue in Crohn's Disease concerns the induction of T regulatory cells in the MLNs. In mice, the induction of regulatory T cells via CD103⁺ MLN DCs is impaired in experimental colitis [56]. Whether the same occurs in Crohn's Disease warrants further investigation.

Summary

Intestinal phagocytes are thought to have an essential role in the perpetuation of Crohn's Disease. Increasing evidence from several studies has shown an imbalance in the phagocyte population in the intestinal lamina propria, with a higher frequency of activated phagocytes expressing cytokines favouring a Th1/Th17 response. However, it is not known what triggers this aberrant immune response. Have DC subsets lost their tolerogenic potential? Do phagocyte subsets have augmented pro-inflammatory functions? Is there an imbalance in the different subpopulations of phagocytes? Have DCs been imprinted with an erroneous function by the local microenvironment? In order to reveal the causes underlying this debilitating disease, the characteristics and functions of DC and macrophage subsets in intestinal tissues and MLNs of patients needs to be studied. This type of information will facilitate treatment and alleviate the suffering of this large and relatively young patient group.

Acknowledgements

The authors are supported by financing from the Swedish Research Council, Västra Götaland LUA/ALF, and Åke Wibergs foundation.

References

1. Baumgart DC, Carding SR: Inflammatory bowel disease: cause and immunobiology. *Lancet* 369, 1627–1640 (2007)
2. Triantafyllidis JK, Nasioulas G et al.: Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies. *Anticancer Res* 29, 2727–2737 (2009)
3. Sartor RB: Microbial influences in inflammatory bowel diseases. *Gastroenterology* 134, 577–594 (2008)
4. Asquith M, Powrie F: An innately dangerous balancing act: intestinal homeostasis, inflammation and colitis-associated cancer. *J Exp Med* 207, 1573–1577 (2010)
5. Sartor RB: Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nature Clin Practice Gastroenterol Hepatol* 3, 390–407 (2006)
6. Rutgeerts P, Goboos K et al.: Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. *Lancet* 338, 771–774 (1991)
7. Harper PH, Lee EC et al.: Role of the faecal stream in the maintenance of Crohn's colitis. *Gut* 26, 279–284 (1985)
8. Smith AM, Rahman FZ et al.: Disordered macrophage cytokine secretion underlies impaired acute inflammation and bacterial clearance in Crohn's disease. *J Exp Med* 206, 1883–1897 (2009)
9. Martinez-Medina M, Aldeguer X et al.: Abnormal microbiota composition in the ileocolonic mucosa of Crohn's disease patients as revealed by polymerase chain reaction-denaturing gradient gel electrophoresis. *Inflamm Bowel Dis* 12, 1136–1145 (2006)
10. Sokol H, Seksik P et al.: Specificities of the fecal microbiota in inflammatory bowel disease. *Inflamm Bowel Dis* 12, 106–111 (2006)
11. Brand S: Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. *Gut* 58, 1152–1167 (2009)
12. Niess JH, Reinecker HC: Dendritic cells in the recognition of intestinal microbiota. *Cell Microbiol* 8, 558–564 (2006)
13. Rescigno M, Di Sabatino A: Dendritic cells in intestinal homeostasis and disease. *J Clin Invest* 119, 2441–2450 (2009)
14. Coombes JL and Powrie F: Dendritic cells in intestinal immune regulation. *Nat Rev Immunol* 8, 435–446 (2008)
15. Smythies LW, Sellers M et al.: Human intestinal macrophages display profound inflammatory anergy despite avid phagocytic and bacteriocidal activity. *J Clin Invest* 115, 66–75 (2005)
16. Tezuka H, Ohteki T: Regulation of intestinal homeostasis by dendritic cells. *Immunol Rev* 234, 247–258 (2010)
17. del Rio M-L, Bernhardt G et al.: Development and functional specialization of CD103⁺ dendritic cells. *Immunol Rev* 234, 268–281 (2010)
18. Schulz O, Jaensson E et al.: Intestinal CD103⁺, but not CX3CR1⁺, antigen sampling cells migrate in lymph and serve classical dendritic cell functions. *J Exp Med* 206, 3101–3114 (2009)

19. Bogunovic M, Ginhoux F et al.: Origin of the lamina propria dendritic cell network. *Immunity* 31, 513–525 (2009)
20. Jaensson E, Uronen-Hansson H et al.: Small intestinal CD103⁺ dendritic cells display unique functional properties that are conserved between mice and humans. *J Exp Med* 205, 2139–2149 (2008)
21. Coombes JL, Siddiqui KR et al.: A functionally specialized population of mucosal CD103⁺ DCs induces Foxp3⁺ regulatory T cells via a TGF- β and retinoic acid-dependent mechanism. *J Exp Med* 204, 1757–1764 (2007)
22. Annacker O, Coombes JL et al.: Essential role for CD103 in the T cell-mediated regulation of experimental colitis. *J Exp Med* 202, 1051–1061 (2005)
23. Siddiqui KRR, Laffont S et al.: E-Cadherin marks a subset of inflammatory dendritic cells that promote T cell-mediated colitis. *Immunity* 32, 557–567 (2010)
24. Varol C, Vallon-Eberhard A et al.: Intestinal lamina propria dendritic cell subsets have different origin and functions. *Immunity* 31, 502–512 (2009)
25. Rogler G, Hausmann M et al.: Isolation and phenotypic characterization of colonic macrophages. *Clin Exp Immunol* 112, 205–215 (1998)
26. Rydström A and Wick MJ: Monocyte recruitment, activation and function in the gut-associated lymphoid tissue during oral *Salmonella* infection. *J. Immunol* 178, 5789–5801 (2007)
27. Silva MA, Quera R et al.: Dendritic cells and toll-like receptors 2 and 4 in the ileum of Crohn's disease patients. *Dig Dis Sci* 53, 1917–1928 (2008)
28. Silva MA, Lopez CB et al.: Characterization and distribution of colonic dendritic cells in Crohn's disease. *Inflamm Bowel Dis* 10, 504–512 (2004)
29. te Velde AA, van Kooyk Y et al.: Increased expression of DC-SIGN⁺IL-12⁺IL-18⁺ and CD83⁺IL-12-IL-18- dendritic cell populations in the colonic mucosa of patients with Crohn's disease. *Eur J Immunol* 33, 143–151 (2003)
30. Verstege MI, ten Kate FJ et al.: Dendritic cell populations in colon and mesenteric lymph nodes of patients with Crohn's disease. *J Histochem Cytochem* 56, 233–241 (2008)
31. Smith PD, Smythies LE et al.: Intestinal macrophages lack CD14 and CD89 and consequently are down-regulated for LPS- and IgA-mediated activities. *J Immunol* 167, 2651–2656 (2001)
32. Kamada N, Hisamatsu T et al.: Unique CD14 intestinal macrophages contribute to the pathogenesis of Crohn disease via IL-23/IFN- γ axis. *J Clin Invest* 118, 2269–2280 (2008)
33. Kamada N, Hisamatsu T et al.: Human CD14⁺ macrophages in intestinal lamina propria exhibit potent antigen-presenting ability. *J Immunol* 183, 1724–1731 (2009)
34. Dillon SM, Rogers LM et al.: Human intestinal lamina propria CD1c⁺ dendritic cells display an activated phenotype at steady state and produce IL-23 in response to TLR7/8 stimulation. *J Immunol* 184, 6612–6621 (2010)
35. Baumgart DC, Thomas S et al.: Exaggerated inflammatory response of primary human myeloid dendritic cells to lipopolysaccharide in patients with inflammatory bowel disease. *Clin Exp Immunol* 157, 423–436 (2009)
36. Matteoli G, Mazzini E et al.: Gut CD103⁺ dendritic cells express indoleamine 2,3-dioxygenase which influences T regulatory/T effector cell balance and oral tolerance induction. *Gut* 59, 595–604 (2010)
37. Beitnes AC, Raki M et al.: Density of CD163⁺ CD11c⁺ dendritic cells increases and CD103(+) dendritic cells decreases in the coeliac lesion. *Scand J Immunol* (2011)
38. Crozat K, Guiton R et al.: The XC chemokine receptor 1 is a conserved selective marker of mammalian cells homologous to mouse CD8 α ⁺ dendritic cells. *J Exp Med* 207, 1283–1292 (2010)
39. Jongbloed SL, Kassianos AJ et al.: Human CD141⁺ (BDCA-3)⁺ dendritic cells (DCs) represent a unique myeloid DC subset that cross-presents necrotic cell antigens. *J Exp Med* 207, 1247–1260 (2010)
40. Poulin LF, Salio M et al.: Characterization of human DNGR-1⁺ BDCA3⁺ leukocytes as putative equivalents of mouse CD8 α ⁺ dendritic cells. *J Exp Med* 207, 1261–1271 (2010)
41. Bachem A, Guttler S et al.: Superior antigen cross-presentation and XCR1 expression define human CD11c⁺CD141⁺ cells as homologues of mouse CD8⁺ dendritic cells. *J Exp Med* 207, 1273–1281 (2010)
42. Raki M, Tollefsen S et al.: A unique dendritic cell subset accumulates in the celiac lesion and efficiently activates gluten-reactive T cells. *Gastroenterology* 131, 428–438 (2006)
43. Dzionek A, Inagaki Y et al.: Plasmacytoid dendritic cells: from specific surface markers to specific cellular functions. *Hum Immunol* 63, 1133–1148 (2002)
44. Johansson-Lindbom B, Svensson M et al.: Functional specialization of gut CD103⁺ dendritic cells in the regulation of tissue-selective T cell homing. *J Exp Med* 202, 1063–1073 (2005)
45. Iliev ID, Spadoni I et al.: Human intestinal epithelial cells promote the differentiation of tolerogenic dendritic cells. *Gut* 58, 1481–1489 (2009)
46. Sakuraba A, Sato T et al.: Th1/Th17 immune response is induced by mesenteric lymph node dendritic cells in Crohn's disease. *Gastroenterology* 137, 1736–1745 (2009)
47. Cobrin GM and Abreu MT: Defects in mucosal immunity leading to Crohn's disease. *Immunol Rev* 206, 277–295 (2005)
48. Casanova JL and Abel L: Revisiting Crohn's disease as a primary immunodeficiency of macrophages. *J Exp Med* 206, 1839–1843 (2009)
49. Hayee B, Rahman FZ et al.: Crohn's disease as an immunodeficiency. *Expert Rev Clin Immunol* 6, 585–596 (2010)
50. Salim SY, Silva MA et al.: CD83⁺CCR7[−] dendritic cells accumulate in the subepithelial dome and internalize translocated *Escherichia coli* HB101 in the Peyer's patches of ileal Crohn's disease. *Am J Pathol* 174, 82–90 (2009)
51. Middel P, Raddatz D et al.: Increased number of mature dendritic cells in Crohn's disease: evidence for a chemokine mediated retention mechanism. *Gut* 55, 220–227 (2006)
52. Perminow G, Reikvam DH et al.: Increased number and activation of colonic macrophages in pediatric patients with untreated Crohn's disease. *Inflamm Bowel Dis* 15, 1368–1378 (2009)
53. Hart AL, Al-Hassi HO et al.: Characteristics of intestinal dendritic cells in inflammatory bowel diseases. *Gastroenterology* 129, 50–65 (2005)
54. Ng SC, Benjamin JL et al.: Relationship between human intestinal dendritic cells, gut microbiota, and disease activity in Crohn's disease. *Inflamm Bowel Dis* (2010)
55. Brand S: Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. *Gut* 58, 1152–1167 (2009)
56. Laffont S, Siddiqui KRR et al.: Intestinal inflammation abrogates the tolerogenic properties of MLN CD103⁺ dendritic cells. *European Journal of Immunology* 40, 1877–1883 (2010)