CD103+ CD11b+ mucosal classical dendritic cells initiate long-term switched antibody responses to flagellin

Antibody responses induced at mucosal and nonmucosal sites demonstrate a significant level of autonomy. Here, we demonstrate a key role for mucosal interferon regulatory factor-4 (IRF4)-dependent CD103+ CD11b+(DP), classical dendritic cells (cDCs) in the induction of T-dependent immunoglobulin G (IgG) and immunoglobulin A (IgA) responses in the mesenteric lymph node (MLN) following systemic immunization with soluble flagellin (sFliC). In contrast, IRF8-dependent CD103+ CD11b− (SP) are not required for these responses. The lack of this response correlated with a complete absence of sFliC-specific plasma cells in the MLN, small intestinal lamina propria, and surprisingly also the bone marrow (BM). Many sFliC-specific plasma cells accumulating in the BM of immunized wild-type mice expressed α4β7+, suggesting a mucosal origin. Collectively, these results suggest that mucosal DP cDC contribute to the generation of the sFliC-specific plasma cell pool in the BM and thus serve as a bridge linking the mucosal and systemic immune system.

Characterization of Murine Intestinal Mesenchymal Stromal Cells

The intestinal mucosa contains numerous and diverse subsets of immune cells that play an essential role in tissue homeostasis, immunity, and inflammation. Immune cells are diffusely distributed throughout the intestinal lamina propria (LP) within a network of mesenchymal stromal cells (MSCs) that are increasingly recognized as regulators of epithelial as well as immune cell development and function. Despite this, our understanding of intestinal LP MSC ontogeny, heterogeneity, and function remains limited. To gain a better understanding of LP MSC heterogeneity, murine small intestinal and colon LP cell suspensions (after removal of the smooth muscle layer) were stained and flow cytometry sorted, removing epithelial (EP-CAM+), endothelial (CD31+), lymphoid tissue associated (BP3+), hematopoietic (CD45+, Ter119+) and glial cells (NCAMhi). Single cell RNA-seq on sorted cells was subsequently performed by DROPseq. Our preliminary results suggest that the LP MSC compartment comprises numerous specialized subsets, a result we are currently confirming by flow cytometry and whole mount immunohistochemical analysis. Future studies aim to assess the ontogeny of these subsets and the potential role of each subset in intestinal immune homeostasis and disease.
Intestinal CD103^+CD11b^+ cDC2 conventional dendritic cells are required for primary CD4^+ T and B cell responses to soluble flagellin

Systemic immunization with soluble flagellin (sFliC) from Salmonella Typhimurium induces mucosal responses, offering potential as an adjuvant platform for vaccines. Moreover, this engagement of mucosal immunity is necessary for optimal systemic immunity, demonstrating an interaction between these two semi-autonomous immune systems. Although TLR5 and CD103^+CD11b^+ cDC2 contribute to this process, the relationship between these is unclear in the early activation of CD4^+ T cells and the development of antigen-specific B cell responses. In this work, we use TLR5-deficient mice and CD11c-cre.Irf4fl/fl mice (which have reduced numbers of cDC2, particularly intestinal CD103^+CD11b^+ cDCs), to address these points by studying the responses concurrently in the spleen and the mesenteric lymph nodes (MLN). We show that CD103^+CD11b^+ cDC2 respond rapidly and accumulate in the MLN after immunization with sFliC in a TLR5-dependent manner. Furthermore, we identify that whilst CD103^+CD11b^+ cDC2 are essential for the induction of primary T and B cell responses in the mucosa, they do not play such a central role for the induction of these responses in the spleen. Additionally, we show the involvement of CD103^+CD11b^+ cDC2 in the induction of Th2-associated responses. CD11c-cre.Irf4fl/fl mice showed a reduced primary FliC-specific Th2-associated IgG1 responses, but enhanced Th1-associated IgG2c responses. These data expand our current understanding of the mucosal immune responses promoted by sFliC and highlights the potential of this adjuvant for vaccine usage by taking advantage of the functionality of mucosal CD103^+CD11b^+ cDC2.

General information
Publication status: Published
Organisations: Department of Micro- and Nanotechnology, University of Birmingham, Ghent University, University of Tokyo, Osaka University, Lund University
Corresponding author: Flores-Langarica, A.
Number of pages: 9
Publication date: 2018
Peer-reviewed: Yes

Publication information
Journal: Frontiers in Immunology
Volume: 9
Article number: 2409
ISSN (Print): 1664-3224
Ratings:
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
Original language: English
Keywords: CDC2, Dendritic cells, Flagellin, Immune response, Mucosa
Electronic versions:
Untitled.pdf
DOIs: 10.3389/fimmu.2018.02409
Source: Scopus
Source-ID: 85055143183
Research output: Contribution to journal › Journal article – Annual report year: 2018 › Research › peer-review

Retinoic Acid Signaling in Stromal Cells Regulates Intestinal Lymphoid Tissue Stromal Development

Intestinal lymphoid tissues such as Peyer’s patches (PP) and intestine-draining mesenteric lymph nodes (MLN) represent major priming sites of intestinal immune activation and are crucial for the maintenance of mucosal immune homeostasis. The architecture of these lymphoid tissues is preserved by a complex three-dimensional network of distinct mesenchyme-derived stromal cells (SC) residing in different environments within the tissue. Besides providing a scaffold to optimize immune cell interactions SC produce key immune cell migratory and survival cues and are thus increasingly recognized as essential regulators of intestinal immune function.

Vitamin A is obtained through the diet and its metabolite, retinoic acid (RA), has emerged as a key regulator of intestinal immune responses by directly inducing gut-tropic T and B cells in PP and MLN, driving de novo generation of regulatory T cells and promoting IgA production. Despite these findings, the impact of RA signaling in intestinal lymphoid SC on PP and MLN SC development and the consequence of these signals on intestinal immune responses remains completely unknown.

To gain a better understanding of the impact of RA signaling in SC we have generated mice whose intestinal lymphoid SC fail to respond to RA. Our preliminary data suggest that the lack of SC-specific RA signaling alters the SC compartment of PP and MLN. Further studies aim to assess the potential role of SC-specific RA signaling in intestinal immune homeostasis and during inflammation.
Retinoic Acid Signaling in Thymic Epithelial Cells Regulates Thymopoiesis

Despite the essential role of thymic epithelial cells (TEC) in T cell development, the signals regulating TEC differentiation and homeostasis remain incompletely understood. In this study, we show a key in vivo role for the vitamin A metabolite, retinoic acid (RA), in TEC homeostasis. In the absence of RA signaling in TEC, cortical TEC (cTEC) and CD80<sup>lo</sup>MHC class II<sup>lo</sup> medullary TEC displayed subset-specific alterations in gene expression, which in cTEC included genes involved in epithelial proliferation, development, and differentiation. Mice whose TEC were unable to respond to RA showed increased cTEC proliferation, an accumulation of stem cell Ag-1<sup>hi</sup> cTEC, and, in early life, a decrease in medullary TEC numbers. These alterations resulted in reduced thymic cellularity in early life, a reduction in CD4 single-positive and CD8 single-positive numbers in both young and adult mice, and enhanced peripheral CD8<sup>+</sup> T cell survival upon TCR stimulation. Collectively, our results identify RA as a regulator of TEC homeostasis that is essential for TEC function and normal thymopoiesis.
Characterization of leukocytes in distinct human intestinal compartments

General information
Publication status: Published
Organisations: National Veterinary Institute, Mucosal Immunology, University Hospital Herlev
Number of pages: 2
Pages: 298-299
Publication date: 2017
Peer-reviewed: Yes

Publication information
Journal: Scandinavian Journal of Immunology
Volume: 86
Issue number: 4
Article number: A-31498
ISSN (Print): 0300-9475
Ratings:
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 2.11 SJR 0.891 SNIP 0.621
Web of Science (2017): Impact factor 2.314
Web of Science (2017): Indexed yes
Original language: English
Source: FindIt
Source-ID: 2391995539
Research output: Contribution to journal › Conference abstract in journal – Annual report year: 2017 › Research › peer-review

Different populations of CD11b+ dendritic cells drive Th2 responses in the small intestine and colon
T-helper 2 (Th2) cell responses defend against parasites. Although dendritic cells (DCs) are vital for the induction of T-cell responses, the DC subpopulations that induce Th2 cells in the intestine are unidentified. Here we show that intestinal Th2 responses against Trichuris muris worms and Schistosoma mansoni eggs do not develop in mice with IRF-4-deficient DCs (IRF-4f/f CD11c-cre). Adoptive transfer of conventional DCs, in particular CD11b-expressing DCs from the intestine, is sufficient to prime S. mansoni-specific Th2 responses. Surprisingly, transferred IRF-4-deficient DCs also effectively prime S. mansoni-specific Th2 responses. Egg antigens do not induce the expression of IRF-4-related genes. Instead, IRF-4f/f CD11c-cre mice have fewer CD11b+ migrating DCs and fewer DCs carrying parasite antigens to the lymph nodes. Furthermore, CD11b+ CD103+ DCs induce Th2 responses in the small intestine, whereas CD11b+ CD103+ DCs perform this role in the colon, revealing a specific functional heterogeneity among intestinal DCs in inducing Th2 responses.

General information
Publication status: Published
Organisations: National Veterinary Institute, Mucosal Immunology, University of Glasgow, Lund University, University of Manchester
Contributors: Mayer, J. U., Demiri, M., Agace, W. W., MacDonald, A. S., Svensson Frej, M., Milling, S. W.
Publication date: 2017
Peer-reviewed: Yes

Publication information
Distinct DC subsets regulate adaptive Th1 and 2 responses during *Trichuris muris* infection

Low- and high-dose infections with the murine large intestinal nematode *Trichuris muris* are associated with induction of adaptive Th1 and Th2 responses, respectively, in mesenteric lymph nodes (MLN). Classical dendritic cells (cDC) accumulate in the large intestinal mucosa and MLN upon *T. muris* infection, yet their role in driving adaptive responses to infection remains largely unknown. We performed low- and high-dose *T. muris* infections of mice deficient in defined cDC subsets to investigate their role in induction of adaptive immune responses. Mice lacking IRF4-dependent cDC failed to clear a high-dose infection and displayed impaired Th2 responses. Conversely, mice lacking IRF8-dependent cDC cleared a low-dose infection and displayed an impaired Th1 response while increased production of Th2 cytokines. Finally, mice lacking both IRF4- and IRF8-dependent cDC were able to generate a Th2 response and clear a low-dose infection. Collectively, these results suggest that IRF4- and IRF8-dependent cDC act antagonistically during *T. muris* infection, and demonstrate that intestinal Th2 responses can be generated towards *T. muris* in the absence of IRF4-dependent cDC.

**Distinct DC subsets regulate adaptive Th1 and 2 responses during *Trichuris muris* infection**

Low- and high-dose infections with the murine large intestinal nematode *Trichuris muris* are associated with induction of adaptive Th1 and Th2 responses, respectively, in mesenteric lymph nodes (MLN). Classical dendritic cells (cDC) accumulate in the large intestinal mucosa and MLN upon *T. muris* infection, yet their role in driving adaptive responses to infection remains largely unknown. We performed low- and high-dose *T. muris* infections of mice deficient in defined cDC subsets to investigate their role in induction of adaptive immune responses. Mice lacking IRF4-dependent cDC failed to clear a high-dose infection and displayed impaired Th2 responses. Conversely, mice lacking IRF8-dependent cDC cleared a low-dose infection and displayed an impaired Th1 response while increased production of Th2 cytokines. Finally, mice lacking both IRF4- and IRF8-dependent cDC were able to generate a Th2 response and clear a low-dose infection. Collectively, these results suggest that IRF4- and IRF8-dependent cDC act antagonistically during *T. muris* infection, and demonstrate that intestinal Th2 responses can be generated towards *T. muris* in the absence of IRF4-dependent cDC.
role in mucosal homeostasis, infection and inflammation. In the current review we discuss the function of intestinal cDC and monocyte-derived MNP, highlighting how these subsets play several non-redundant roles in the regulation of intestinal immune responses. While much remains to be learnt, recent findings also underline how the various populations of MNP adapt to deal with the challenges specific to their environment. Understanding these processes should help target individual subsets for ‘fine tuning’ immunological responses within the intestine, a process that maybe of relevance both for the treatment of inflammatory bowel disease (IBD) and for optimized vaccine design.

Eosinophils are key regulators of perivascular adipose tissue and vascular functionality
Obesity impairs the relaxant capacity of adipose tissue surrounding the vasculature (PVAT) and has been implicated in resultant obesity-related hypertension and impaired glucose intolerance. Resident immune cells are thought to regulate adipocyte activity. We investigated the role of eosinophils in mediating normal PVAT function. Healthy PVAT elicits an anti-contractile effect, which was lost in mice deficient in eosinophils, mimicking the obese phenotype, and was restored upon eosinophil reconstitution. Ex vivo studies demonstrated that the loss of PVAT function was due to reduced bioavailability of adiponectin and adipocyte-derived nitric oxide, which was restored after eosinophil reconstitution. Mechanistic studies demonstrated that adiponectin and nitric oxide are released after activation of adipocyte-expressed β3 adrenoceptors by catecholamines, and identified eosinophils as a novel source of these mediators. We conclude that adipose tissue eosinophils play a key role in the regulation of normal PVAT anti-contractile function.
GP2 is selectively expressed by small intestinal CD103+CD11b+ cDC

The functionality of tissue cDC is regulated, at least in part, by the signals these cells receive within their local environment. For example, we and others, have demonstrated that murine small intestinal but not colonic cDC are imprinted with an ability to generate the Vitamin A metabolite, retinoic acid, and thus an enhanced capacity to drive the generation of small intestinal homing T cells. Here we demonstrate that Glycoprotein 2 (GP2), a GPI-anchored protein previously shown to be selectively expressed by M-cells and to act as a receptor for type 1 fimbriated bacteria, is expressed by a large proportion of IRF4-dependent cDC in the small intestine but not in other tissues. While surface expression of GP2 by small intestinal CD103+CD11b+ cDC was independent of lymphocytes and MyD88 signaling, administration of broad spectrum antibiotics increased the proportion of GP2+CD103+CD11b+ cDC in the small intestine. Moreover, GP2 expressing cDC in the small intestine were dramatically reduced in the setting of intestinal inflammation. We have previously shown that mice with an IRF4 deletion in CD11c+ cells (Cd11c-cre.Irf4 fl/fl mice) have reduced numbers of small intestinal CD103+CD11b+ cDC. Interestingly, we found that GP2+ CD103+CD11b+ cDC were dramatically reduced in these mice. Finally, to address the in vivo role of GP2 expression by cDC, we have generated mice with a selective deletion of GP2 in CD103+CD11b+ cDC (huLangerin-cre.gp2 fl/fl mice). Results from these ongoing studies will be presented.

General information
Publication status: Published
Organisations: National Veterinary Institute, Mucosal Immunology, Lund University, Yokohama City University
Contributors: Müller-Luda, K., Ahmadi, F., Ohno, H., Kotarsky, K., Agace, W. W.
Publication date: 2017
Peer-reviewed: Yes
Electronic versions: 2017_Scandinavian_Journal_of_Immunology_1_292.pdf
Source: FindIt
Source-ID: 2391995507
Research output: Contribution to conference › Conference abstract for conference – Annual report year: 2017 › Research › peer-review

Irf4-dependent CD103+CD11b+ dendritic cells and the intestinal microbiome regulate monocyte and macrophage activation and intestinal peristalsis in postoperative ileus

Objective: Postoperative ileus (POI), the most frequent complication after intestinal surgery, depends on dendritic cells (DCs) and macrophages. Here, we have investigated the mechanism that activates these cells and the contribution of the intestinal microbiota for POI induction. Design: POI was induced by manipulating the intestine of mice, which selectively lack DCs, monocytes or macrophages. The disease severity in the small and large intestine was analysed by determining the distribution of orally applied fluorescein isothiocyanate-dextran and by measuring the excretion time of a retrogradely inserted glass ball. The impact of the microbiota on intestinal peristalsis was evaluated after oral antibiotic treatment. Results: We found that Cd11c-Cre+ Irf4+ mice lack CD103+CD11b+ DCs, a DC subset unique to the intestine whose function is poorly understood. Their absence in the intestinal muscularis reduced pathogenic inducible nitric oxide synthase (iNOS) production by monocytes and macrophages and ameliorated POI. Pathogenic iNOS was produced in the jejunum by resident Ly6C+ macrophages and infiltrating chemokine receptor 2-dependent Ly6C+ monocytes, but in the colon only by the latter demonstrating differential tolerance mechanisms along the intestinal tract. Consistently, depletion of both cell subsets reduced small intestinal POI, whereas the depletion of Ly6C+ monocytes alone was sufficient to prevent large intestinal POI. The differential role of monocytes and macrophages in small and large intestinal POI suggested a potential role of the intestinal microbiota. Indeed, antibiotic treatment reduced iNOS levels and ameliorated POI. Conclusions: Our findings reveal that CD103+CD11b+ DCs and the intestinal microbiome are a prerequisite for the activation of intestinal monocytes and macrophages and for dysregulating intestinal motility in POI.

General information
Publication status: Published
Organisations: National Veterinary Institute, Mucosal Immunology, University of Duisburg-Essen, University Hospital Essen, Weizmann Institute of Science, Lund University, University of Bonn
Regionalized Development and Maintenance of the Intestinal Adaptive Immune Landscape

The intestinal immune system has the daunting task of protecting us from pathogenic insults while limiting inflammatory responses against the resident commensal microbiota and providing tolerance to food antigens. This role is particularly impressive when one considers the vast mucosal surface and changing landscape that the intestinal immune system must monitor. In this review, we highlight regional differences in the development and composition of the adaptive immune landscape of the intestine and the impact of local intrinsic and environmental factors that shape this process. To conclude, we review the evidence for a critical window of opportunity for early-life exposures that affect immune development and alter disease susceptibility later in life.

General information
Publication status: Published
Organisations: National Veterinary Institute, Mucosal Immunology, University of Calgary
Contributors: Agace, W. W., McCoy, K. D.
Number of pages: 17
Pages: 532-548
Publication date: 2017
Peer-reviewed: Yes

Bibliographical note
This is an Open Access article distributed in accordance with the Creative Commons attribution Non Commercial (CC BY-NC 4.0) license.
Source: Findit
Source-ID: 2371505377
Research output: Contribution to journal › Journal article – Annual report year: 2017 › Research › peer-review

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The role of retinoic acid signaling in thymic function

Retinoic acid (RA) is a vitamin A metabolite and member of the large family of retinoids that have been used in treatment of various forms of cancer and skin disorders. Also, vitamin A deficiency is associated with impaired ability to fight infections and RA has been shown to shape peripheral immune responses. However, little is known about the role of RA in the development of immune cells. We are currently investigating the role of RA signaling in thymic function. In the thymus, thymic epithelial cells (TEC) are providing the specialized microenvironment that supports T cell development and proper TEC maturation and homeostasis is required for the generation of a functional T cell pool. TEC development and differentiation is dependent on crosstalk with immune and stromal cells in the thymus and previous work of our group has suggested RA as a potential key player in this process. To study the role of RA signaling in TEC homeostasis and function in vivo we are using a transgenic mouse model where RA signaling is blocked in the TEC compartment. Thereby we could show that RA controls TEC subset composition and maturation postnataally, preferably in the cortical TEC compartment. Block of RA signaling in TEC also affects T cell development and results in reduced numbers of single positive (SP) thymocytes and naive CD8+ T cells in the periphery. These findings provide first in vivo evidence for a role of RA signaling in the adult thymus regarding TEC function and T cell development.

A reduced population of CD103+CD11b+ dendritic cells has a limited impact on oral Salmonella infection

CD103(+)CD11b(+) dendritic cells (DC) are the major migratory DC subset in the small intestine lamina propria (siLP) and their survival is dependent on the transcription factor interferon regulatory factor 4 (IRF4). Mice with a DC-specific deletion of irf4 (CD11c-cre.Irf4 mice) have reduced mucosal CD103(+)CD11b(+) DC and altered T cell differentiation to protein antigen. The influence of CD103(+)CD11b(+) DC on oral infection with the gastrointestinal pathogen Salmonella, however, is poorly understood and is investigated here. We show that, despite being infected with Salmonella, CD11c-cre.Irf4 mice (called Cre(+) mice) conserve the reduction in CD103(+)CD11b(+) DC observed in naive Cre(+) mice, particularly in the mesenteric lymph nodes (MLN) but also in the siLP at day 3 post infection. Moreover, Salmonella-infected Cre(+) mice have a similar bacterial burden in intestinal tissues (siLP, MLN and Peyer's patches) as well as the spleen compared to infected Cre-controls. The T cell compartment, including the frequency of IFN-gamma and IL-17-producing T cells, is not altered in intestinal tissues of Salmonella-infected Cre(+) mice relative to infected Cre-controls. In addition, no difference between infected Cre(+) and Cre-mice was observed in either the concentration of IL-6 or IL-17 in whole tissue lysates of siLP, MLN or Peyer's patches or in the serum concentration of Salmonella-specific IgG and IgM. Overall the data suggest that the reduction of CD103(+)CD11b(+) DC in Cre(+) mice has little if any impact on Salmonella burden in infected tissues or eliciting effector functions important in host survival at later stages of the infection. (C) 2016 European Federation of Immunological Societies. Published by Elsevier B.V. All rights reserved.
Evidence for a dual function of monocyte-derived mononuclear phagocytes during chronic intestinal inflammation

Mononuclear phagocytes derived from tissue-infiltrating monocytes play diverse roles in immunity, ranging from pathogen killing to immune regulation. We and others showed that, upon recruitment to the intestinal mucosa, the differentiation of Ly6Chi monocytes into phagocytes with anti- versus pro-inflammatory phenotypes can be shaped by the steady state versus inflammatory local tissue environment. However, the in vivo functions of these monocyte-derived phagocytes (MDP) remain poorly understood. Using the T cell transfer colitis model, we now show that MDP represent more than 85% of the total antigen presenting cells pool in the inflamed intestinal mucosa. However, surprisingly, mice deficient for the chemokine receptor CCR2, which exhibit highly decreased amounts of intestinal MDP, develop an intestinal pathology similar to their wild type littermates. Preliminary experiments using the anti-CD40 colitis model suggest a dual and time-
restricted contribution of MDP during the development and healing phases of the disease.

**General information**
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology
Contributors: Rivollier, A. M. C., Pool, L., Frising, U., Danilova, E., Agace, W. W.
Number of pages: 1
Publication date: 2016
Peer-reviewed: Yes
Event: Abstract from Cell Symposium: 100 years of phagocytes, Sicily, Italy.
Research output: Contribution to conference » Conference abstract for conference – Annual report year: 2016 » Research » peer-review

**IL-18Rα-deficient CD4+ T cells induce intestinal inflammation in the CD45RBhi transfer model of colitis despite impaired innate responsiveness**

IL-18 has been implicated in inflammatory bowel disease (IBD), however its role in the regulation of intestinal CD4+ T-cell function remains unclear. Here we show that murine intestinal CD4+ T cells express high levels of IL-18Rα and provide evidence that IL-18Rα expression is induced on these cells subsequent to their entry into the intestinal mucosa. Using the CD45RBhi T-cell transfer colitis model, we show that IL-18Rα is expressed on IFN-γ+, IL-17+ and IL-17+IFN-γ+ effector CD4+ T cells in the inflamed colonic lamina propria (cLP) and mesenteric lymph node (MLN) and is required for the optimal generation and/or maintenance of IFN-γ-producing cells in the cLP. In the steady state and during colitis, TCR-independent cytokine-induced IFN-γ and IL-17 production by intestinal CD4+ T cells was largely IL-18Rα-dependent. Despite these findings however, IL-18Rα−deficient CD4+ T cells induced comparable intestinal pathology to WT CD4+ T cells. These findings suggest that IL-18-dependent cytokine induced activation of CD4+ T cells is not critical for the development of T-cell-mediated colitis.

**General information**
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University
Pages: 1371-1382
Publication date: 2016
Peer-reviewed: Yes

**Publication information**
Journal: European Journal of Immunology
Volume: 46
Issue number: 6
ISSN (Print): 0014-2980
Ratings:
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.61 SJR 2.525 SNIP 0.927
Web of Science (2016): Impact factor 4.227
Web of Science (2016): Indexed yes
Original language: English
Electronic versions:
Holmkvist_et_al_2016_European_Journal_of_Immunology.pdf
DOIs:
10.1002/eji.201545957
Source: FindIt
Source-ID: 230344460
Research output: Contribution to journal » Journal article – Annual report year: 2016 » Research » peer-review

**IRF8 dependent classical dendritic cells are essential for intestinal T cell homeostasis**

The role of dendritic cells (DCs) in intestinal immune homeostasis remains incompletely defined. Here we show that mice lacking IRF8 dependent DCs have reduced numbers of T cells in the small intestine (SI), but not large intestine (LI), including an almost complete absence of SI CD8ab+ andCD4+CD8aa+ T cells; the latter requiring b8 integrin expression by migratory IRF8 dependent CD103+CD11b+ DCs. SI homing receptor induction was impaired during T cell priming in mesenteric lymph nodes (MLN), which correlated with a reduction in aldehyde dehydrogenase activity by SI derived MLN DCs, and inefficient T cell localization to the SI. Finally, mice with a DC deletion in IRF8 lacked intestinal T helper 1 (Th1) cells, and failed to support Th1 cell differentiation in MLN and mount Th1 responses to *Trichuris muris* infection. Collectively these results highlight multiple non-redundant roles for IRF8 dependent DCs in the maintenance of intestinal T cell homeostasis.
IRF8-dependent DCs play a key role in the regulation of CD8 T cell responses to epithelial-derived antigen in the steady state but not in inflammation

Along the process of epithelial self-renewal, antigens derived from apoptotic intestinal epithelial cells (IECs) are taken up by antigen presenting cells (APCs), transported to the gut-draining lymph nodes and cross-presented to CD8 T cells. In steady state, rapid tolerization of CD8 T cells reactive towards epithelial-derived antigens is crucial to maintain tissue homeostasis. In contrast, infection of IECs by intracellular pathogens requires induction of cytotoxic CD8 T cells (CTLs) towards epithelial-associated, pathogen-derived antigens. Currently, little is known about the regulation of CD8 T cells by intestinal APCs in these two different contexts. Since IRF8-dependent dendritic cells (IRF8-DCs) have superior cross-presenting capabilities, we aimed to investigate their role in this process. IFABP-Ova mice, expressing the model-antigen Ovalbumin (Ova) in IECs, were used as recipients to set up chimeras using either CD11c-cre.Irf8^fl/fl bone marrow, which
cannot generate IRF8-DCs, or crenegative Irf8(−/−) control bone marrow. Whereas transfer of Ova-specific CD8 T cells (OT-I cells) to steady state control chimeras resulted in their rapid tolerization, OT-I cells transferred to CD11ccre.Irf8(−/−) chimeras spontaneously developed into CTLs, causing epithelial destruction and intestinal inflammation. However, when the TLR7-ligand R848 was applied as an inflammatory trigger mimicking viral infection in addition to OT-I transfer, expansion of CTLs occurred at similar rates in both, CD11ccre.Irf8(−/−) and control chimeras. Taken together, this demonstrates that IRF8-DCs are crucial for therapeutically tolerizing CD8 T cells reactive towards epithelial-derived antigen in steady state, but are not essential for the induction of CTLs in an inflammatory setting such as found in infection.

General information
Publication status: Published
Organisations: National Veterinary Institute, Mucosal Immunology, Lund University, Inflammation Research Center (IRC)
Pages: 788-788
Publication date: 2016
Peer-reviewed: Yes

Publication information
Journal: European Journal of Immunology
Volume: 46
Issue number: Suppl. 1
ISSN (Print): 0014-2980
Ratings:
  - BFI (2016): BFI-level 1
  - Scopus rating (2016): CiteScore 3.61 SJR 2.525 SNIP 0.927
  - Web of Science (2016): Impact factor 4.227
  - Web of Science (2016): Indexed yes
Original language: English
Electronic versions:
2016-European_Journal_of_Immunology4
Research output: Contribution to journal › Conference abstract in journal – Annual report year: 2017 › Research › peer-review

IRF8 Transcription Factor Controls Survival and Function of Terminally Differentiated Conventional and Plasmacytoid Dendritic Cells, Respectively
Interferon regulatory factor-8 (IRF8) has been proposed to be essential for development of monocytes, plasmacytoid dendritic cells (pDCs) and type 1 conventional dendritic cells (cDC1s) and remains highly expressed in differentiated DCs. Transcription factors that are required to maintain the identity of terminally differentiated cells are designated "terminal selectors." Using BM chimeras, conditional Irf8(−/−) mice and various promoters to target Cre recombinase to different stages of monocyte and DC development, we have identified IRF8 as the terminal selector of the cDC1 lineage controlling survival in monocytes. IRF8 was necessary during early but not late development. Complete or late deletion of IRF8 had no effect on pDC development or survival but altered their phenotype and gene-expression profile leading to increased T cell stimulatory function but decreased type 1 interferon production. Thus, IRF8 differentially controls the survival and function of terminally differentiated monocytes, cDC1s, and pDCs.

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Ghent University, Johannes Gutenberg University Mainz, CNRS
Number of pages: 15
Pages: 626-640
Publication date: 2016
Peer-reviewed: Yes

Publication information
Journal: Immunity
Volume: 45
Issue number: 3
ISSN (Print): 1074-7613
Ratings:
  - BFI (2016): BFI-level 2
  - Scopus rating (2016): CiteScore 17.17 SJR 16.957 SNIP 4.635
IRF8 Transcription-Factor-Dependent Classical Dendritic Cells Are Essential for Intestinal T Cell Homeostasis

The role of dendritic cells (DCs) in intestinal immune homeostasis remains incompletely defined. Here we show that mice lacking IRF8 transcription-factor-dependent DCs had reduced numbers of T cells in the small intestine (SI), but not large intestine (LI), including an almost complete absence of SI CD8αβ+ and CD4+CD8αα+ T cells; the latter requiring β8 integrin expression by migratory IRF8 dependent CD103+CD11b- DCs. SI homing receptor induction was impaired during T cell priming in mesenteric lymph nodes (MLN), which correlated with a reduction in aldehyde dehydrogenase activity by SI-derived MLN DCs, and inefficient T cell localization to the SI. These mice also lacked intestinal T helper 1 (Th1) cells, and failed to support Th1 cell differentiation in MLN and mount Th1 cell responses to Trichuris muris infection. Collectively these results highlight multiple non-redundant roles for IRF8 dependent DCs in the maintenance of intestinal T cell homeostasis.

Long-term persistence of human donor alveolar macrophages in lung transplant recipients

Background Alveolar macrophages (AMFs) are critical regulators of lung function, and may participate in graft rejection following lung transplantation. Recent studies in experimental animals suggest that most AMFs are self-maintaining cells of embryonic origin, but knowledge about the ontogeny and life span of human AMFs is scarce. Methods To follow the origin and longevity of AMFs in patients with lung transplantation for more than 100 weeks, we obtained transbronchial biopsies from 10 gender-mismatched patients with lung transplantation. These were subjected to combined in situ hybridisation for X/Y chromosomes and immunofluorescence staining for macrophage markers. Moreover, development of AMFs in humanised mice reconstituted with CD34+ umbilical cord-derived cells was assessed. Results The number of donor-derived AMFs was unchanged during the 2 year post-transplantation period. A fraction of the AMFs proliferated locally, demonstrating that at least a subset of human AMFs have the capacity to self-renew. Lungs of humanised mice were found to abundantly contain populations of human AMFs expressing markers compatible with a monocyte origin.
Moreover, in patients with lung transplantation we found that recipient monocytes seeded the alveoli early after transplantation, and showed subsequent phenotypical changes consistent with differentiation into proliferating mature AMFs. This resulted in a stable mixed chimerism between donor and recipient AMFs throughout the 2-year period.

Conclusions The finding that human AMFs are maintained in the lung parenchyma for several years indicates that pulmonary macrophage transplantation can be a feasible therapeutic option for patients with diseases caused by dysfunctional AMFs. Moreover, in a lung transplantation setting, long-term persistence of donor AMFs may be important for the development of chronic graft rejection.

Macrophage and dendritic cell subsets in IBD: ALDH^+ cells are reduced in colon tissue of patients with ulcerative colitis regardless of inflammation

Disruption of the homeostatic balance of intestinal dendritic cells (DCs) and macrophages (MQs) may contribute to inflammatory bowel disease. We characterized DC and MQ populations, including their ability to produce retinoic acid, in clinical material encompassing Crohn’s ileitis, Crohn’s colitis and ulcerative colitis (UC) as well as mesenteric lymph nodes (MLNs) draining these sites. Increased CD14^{+}DR^{int} MQs characterized inflamed intestinal mucosa while total CD14^{+} or CD1c^{+} DCs numbers were unchanged. However, CD103^{+} DCs, including CD14^{+}CD103^{+} and CD1c^{+}CD103^{+} DCs, were reduced in inflamed intestine. In MLNs, two CD14^{+} DC populations were identified: CD11c^{int}HLADR^{hi} and CD11c^{hi}HLADR^{int} cells. A marked increase of CD11c^{hi}HLADR^{int} DC, particularly DR^{hi}CD1c^{+} DCs, characterized MLNs draining inflamed intestine. The fraction of DC and MQ populations expressing aldehyde dehydrogenase (ALDH) activity, reflecting retinoic acid synthesis, in UC colon, both in active disease and remission, were reduced compared to controls and inflamed Crohn’s colon. In contrast, no difference in the frequency of ALDH^{+} cells among blood precursors was detected between UC patients and non-inflamed controls. This suggests that ALDH activity in myeloid cells in the colon of UC patients, regardless of whether the disease is active or in remission, is influenced by the intestinal environment.
Retinoic acid signalling is required for the pathogenicity of effector CD4+ T cells during the development of intestinal inflammation

The vitamin A metabolite retinoic acid (RA) seems to be a double-edge sword in CD4+ T cell biology, sustaining the development of foxp3+ Treg cells, but also being essential for the stability of the Th1 lineage. Here we explored the role of RA signalling in CD4+ T cells during the development of intestinal inflammation in the T cell transfer colitis model. RA signalling-deficient CD4+ T cells are less potent at inducing intestinal inflammation compared to their RA signalling-proficient counterparts and exhibit a differentiation skewing towards more IL-17+ and foxp3+ cells, while their capacity to differentiate into Th1 cells is compromised. In vitro studies confirm the inefficacy of RA signalling-deficient T cells to generate bona fide Th1 cells and demonstrate their aberrant increased RORγt expression, while their Th17 differentiation remains unaffected. Surprisingly, RA signalling-deficient and –proficient Treg cells are equally competent to inhibit colitis development. Together our results indicate that RA, through its receptor RARα, negatively regulates the early expansion of CD4+ T cells during colitis and is necessary for the generation of colitogenic Th1/Th17 cells, while it is dispensable for the protective function of Treg cells. We are currently deciphering the mechanisms of these effects of RA on CD4+ T cells.

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University
Contributors: Rivollier, A. M. C., Pool, L., Frising, U., Wendland, K., Agace, W. W.
Number of pages: 1
Publication date: 2016
Peer-reviewed: Yes
Event: Abstract from 10th European Mucosal Immunology Group meeting, Copenhagen, Denmark.
Research output: Contribution to conference › Conference abstract for conference – Annual report year: 2016 › Research › peer-review

A major population of mucosal memory CD4+ T cells, coexpressing IL-18Rα and DR3, display innate lymphocyte functionality

Mucosal tissues contain large numbers of memory CD4+ T cells that, through T-cell receptor-dependent interactions with antigen-presenting cells, are believed to have a key role in barrier defense and maintenance of tissue integrity. Here we identify a major subset of memory CD4+ T cells at barrier surfaces that coexpress interleukin-18 receptor alpha (IL-18Rα) and death receptor-3 (DR3), and display innate lymphocyte functionality. The cytokines IL-15 or the DR3 ligand tumor necrosis factor (TNF)-like cytokine 1A(TL1a) induced memory IL-18Ra+DR3+CD4+ T cells to produce interferon-gamma, TNF-α, IL-6, IL-13, granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-22 in the presence of IL-12/IL-18. TL1a and IL-15-mediated cytokine induction required the presence of IL-18, whereas induction of IL-5, IL-13, GM-CSF, and IL-22 was IL-12 independent. IL-18Ra+DR3+CD4+ T cells with similar functionality were present in human skin, nasal polyps, and, in particular, the intestine, where in chronic inflammation they localized with IL-18-producing cells in lymphoid aggregates. Collectively, these results suggest that human memory IL-18Ra+DR3+CD4+ T cells may contribute to antigen-independent innate responses at barrier surfaces.

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University, Novo Nordisk AS, Skåne University Hospital
Number of pages: 14
Pages: 545-558
Publication date: 2015
Peer-reviewed: Yes
CCR2⁺CD103⁻ intestinal dendritic cells develop from DC-committed precursors and induce interleukin-17 production by T cells

The identification of intestinal macrophages (mφs) and dendritic cells (DCs) is a matter of intense debate. Although CD103⁺ mononuclear phagocytes (MPs) appear to be genuine DCs, the nature and origins of CD103⁻ MPs remain controversial. We show here that intestinal CD103⁻CD11b⁺ MPs can be separated clearly into DCs and mφs based on phenotype, gene profile, and kinetics. CD64⁻CD103⁻CD11b⁺ MPs are classical DCs, being derived from Flt3 ligand-dependent, DC-committed precursors, not Ly6Chi monocytes. Surprisingly, a significant proportion of these CD103⁻CD11b⁺ DCs express CCR2 and there is a selective decrease in CD103⁻CD11b⁺ DCs in mice lacking this chemokine receptor. CCR2⁺CD103⁻ DCs are present in both the murine and human intestine, drive interleukin (IL)-17a production by T cells in vitro, and show constitutive expression of IL-12/IL-23p40. These data highlight the heterogeneity of intestinal DCs and reveal a bona fide population of CCR2⁺ DCs that is involved in priming mucosal T helper type 17 (Th17) responses.
CCR9 Is Not Required for the Homing of Pro-inflammatory Effector T cells, but is Crucial for Recruitment and Expansion of FoxP3+ CD8+ Tregs in the Small Intestine

Chemokine receptor 9 (CCR9) is required for the homeostatic recruitment of T cells to the mucosa of the small intestine. Accordingly, CCR9 has been suggested as a potential target to inhibit the recruitment of proinflammatory effector T cells (Teff) in inflammatory bowel disease (IBD). Since the contribution of CCR9 to the recruitment of Teff in inflammation is not entirely clear, we aimed to address this question using IFABP-tOva mice. These mice express Ovalbumin (Ova) specifically in small intestinal epithelial cells, which allows triggering of acute inflammation following transfer of Ova-specific CD8+ T cells (OT-I cells) and adjuvant treatment. Strikingly, intestinal inflammation in IFABP-tOva mice could also be triggered following transfer of CCR9-deficient OT-I cells, demonstrating that CCR9 is not required for homing of Teff cells. Interestingly, OTI cells transferred to IFABP-tOva mice did not only differentiate into Teff, but also into FoxP3+ CD8+ Tregs, which in contrast to Teff cells expressed high levels of CCR9. Indeed, recruitment and expansion of this regulatory subset in the small intestine was strongly dependent on CCR9. Hence, our data show that Teff and regulatory T cell subsets use distinct mechanisms for migration to the small intestine and suggest that inhibition of CCR9 in IBD could be more harmful than useful.

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University
Contributors: Gomez-Casado, C., Joeris, T., Holmkvist, P., Agace, W. W.
Number of pages: 1
Publication date: 2015
Peer-reviewed: Yes
Event: Abstract from 17th International Congress of Mucosal Immunology, Berlin, Germany.
Electronic versions:
AbstractCCR9_Poster_Berlin_CGC.docx
Research output: Contribution to conference › Conference abstract for conference – Annual report year: 2015 › Research › peer-review

CCRL1/ACKR4 is expressed in key thymic microenvironments but is dispensable for T lymphopoiesis at steady state in adult mice

Thymus colonisation and thymocyte positioning are regulated by interactions between CCR7 and CCR9, and their respective ligands, CCL19/CCL21 and CCL25. The ligands of CCR7 and CCR9 also interact with the atypical receptor CCRL1 (also known as ACKR4), which is expressed in the thymus and has recently been reported to play an important role in normal alpha beta T-cell development. Here, we show that CCRL1 is expressed within the thymic cortex, predominantly by MHC-IIlowCD40- cortical thymic epithelial cells and at the subcapsular zone by a population of podoplanin+ thymic epithelial cells in mice. Interestingly, CCRL1 is also expressed by stromal cells which surround the pericytes of vessels at the corticomedullary junction, the site for progenitor cell entry and mature thymocyte egress from the thymus. We show that CCRL1 suppresses thymocyte progenitor entry into the thymus, however, the thymus size and cellularity are the same in adult WT and CCRL1-/- mice. Moreover, CCRL1-/- mice have no major perturbations in T-cell populations at different stages of thymic differentiation and development, and have a similar rate of thymocyte migration into the blood. Collectively, our findings argue against a major role for CCRL1 in normal thymus development and function.

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, University of Birmingham, University of Glasgow, Lund University
Pages: 574-583
Publication date: 2015
Peer-reviewed: Yes

Publication information
Journal: European Journal of Immunology
Volume: 45
Issue number: 2
ISSN (Print): 0014-2980
Ratings:
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 3.85 SJR 2.568 SNIP 0.941
Web of Science (2015): Impact factor 4.179
Web of Science (2015): Indexed yes
Context dependent development of lymphoid organ mesenchymal subsets from BP3^Gp38^PDGFRβ^α^CD34^vascular adventitial precursors

Lymphoid associated mesenchymal stromal cells are believed to play essential roles in immune and organ homeostasis however our knowledge regarding the functional heterogeneity and ontogeny of these cells remains limited.

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, University of Birmingham, Lund University
Number of pages: 1
Publication date: 2015
Peer-reviewed: Yes
Event: Abstract from 1st International Venice Thymus Meeting, San Servolo Island, Italy.
Electronic versions: poster_venice_K_Sitnik.pdf

Involvement of IRF4 dependent dendritic cells in T cell dependent colitis

Inflammatory Bowel Disease (IBD) is a chronic non-curable inflammatory disease of the intestine that affects as many as 1.4 million persons in the United States and 2.2 million persons in Europe. IBD results from abnormal immune response to bacterial components of the commensal microflora in genetically susceptible individuals and pathogenic CD4^T cells, which accumulate in the inflamed mucosa, are believed to be key drivers of the disease. While dendritic cells (DCs) are important in the priming of intestinal adaptive immunity and tolerance their role in the initiation and perpetuation of chronic intestinal inflammation remains unclear. In the current study we used the CD45RB^hi^ T cell transfer model of colitis to determine the role of IRF4 dependent DCs in intestinal inflammation. In this model naïve CD4^ T cells when transferred into RAG^-/-^ mice, proliferate and expand in response to bacterial derived luminal antigen, localize to the intestinal mucosa and induce colitis. Adoptive transfer of naïve T cells into CD11cCre.IRF4^flo/flo^RAG-1^-/-^ mice resulted in reduced monocyte recruitment to the intestine and mesenteric lymph nodes (MLN) compared to Cre^-^ controls. Inflammatory cytokines including IFNγ, TNFα and IL-6 also were reduced in the serum and intestinal tissues of these mice. Additionally CD11cCre.IRF4^flo/flo^RAG-1^-/-^ mice displayed significantly reduced numbers of CD4^ T cells in intestinal draining mesenteric lymph nodes and spleen but not the colonic lamina propria. Collectively these results suggest an important role for Irf4 dependent DCs in T cell driven colitis.

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University
Contributors: Pool, L., Rivollier, A. M. C., Agace, W. W.
Number of pages: 1
Publication date: 2015
Peer-reviewed: Yes
Event: Abstract from Keystone Symposia on Molecular and Cellular Biology - Dendritic Cells and Macrophages Reunited, Montreal, Canada.
Electronic versions: Involvement_of_IRF4_dependent_dendritic_cells_in_T_cell_dependent_colitis.docx

Involvement of IRF4 dependent dendritic cells in T cell dependent colitis

Inflammatory Bowel Disease (IBD) is a chronic non-curable inflammatory disease of the intestine that affects as many as 1.4 million persons in the United States and 2.2 million persons in Europe. IBD results from abnormal immune response to bacterial components of the commensal microflora in genetically susceptible individuals and pathogenic CD4^T cells, which accumulate in the inflamed mucosa, are believed to be key drivers of the disease. While dendritic cells (DCs) are important in the priming of intestinal adaptive immunity and tolerance their role in the initiation and perpetuation of chronic intestinal inflammation remains unclear. In the current study we used the CD45RB^hi^ T cell transfer model of colitis to
determine the role of IRF4 dependent DCs in intestinal inflammation. In this model naïve CD4+ T cells when transferred into RAG-/- mice, proliferate and expand in response to bacterial derived luminal antigen, localize to the intestinal mucosa and induce colitis. Adoptive transfer of naïve T cells into CD11cCre.IRF4fl/fl.RAG-1-/- mice resulted in reduced monocyte recruitment to the intestine and mesenteric lymph nodes (MLN) compared to Cre- controls. Inflammatory cytokines including IFNγ, TNFα and IL-6 also were reduced in the serum and intestinal tissues of these mice. Additionally CD11cCre.IRF4fl/fl.RAG-1-/- mice displayed significantly reduced numbers of CD4+ T cells in intestinal draining mesenteric lymph nodes and spleen but not the colonic lamina propria. Collectively these results suggest an important role for IRf4 dependent DCs in T cell driven colitis.

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University
Contributors: Pool, L., Rivollier, A. M. C., Agace, W. W.
Number of pages: 1
Publication date: 2015
Peer-reviewed: Yes
Event: Abstract from 17th International Congress of Mucosal Immunology, Berlin, Germany.
Electronic versions:
Involvement_of_IRF4_dependent_dendritic_cells_in_T_celldependent_colitis.docx
Research output: Contribution to conference › Conference abstract for conference – Annual report year: 2015 › Research › peer-review

Involvement of neurons and retinoic acid in lymphatic development: new insights in increased nuchal translucency

OBJECTIVE:
Increased nuchal translucency originates from disturbed lymphatic development. Abnormal neural crest cell (NCC) migration may be involved in lymphatic development. Because both neuronal and lymphatic development share retinoic acid (RA) as a common factor, this study investigated the involvement of NCCs and RA in specific steps in lymphatic endothelial cell (LEC) differentiation and nuchal edema, which is the morphological equivalent of increased nuchal translucency.

METHODS:
Mouse embryos in which all NCCs were fluorescently labeled (Wnt1-Cre;Rosa26eYfp ), reporter embryos for in vivo RA activity (DR5-luciferase) and embryos with absent (Raldh2-/- ) or in utero inhibition of RA signaling (BMS493) were investigated. Immunofluorescence using markers for blood vessels, lymphatic endothelium and neurons was applied. Flow cytometry was performed to measure specific LEC populations.

RESULTS:
Cranial nerves were consistently close to the jugular lymph sac (JLS), in which NCCs were identified. In the absence of RA synthesis, enlarged JLS and nuchal edema were observed. Inhibiting RA signaling in utero resulted in a significantly higher amount of precursor-LECs at the expense of mature LECs and caused nuchal edema.

CONCLUSIONS:
Neural crest cells are involved in lymphatic development. RA is required for differentiation into mature LECs. Blocking RA signaling in mouse embryos results in abnormal lymphatic development and nuchal edema.

General information
Publication status: Published
Organisations: Lund University, VU University Medical Centre, Institut de Génétique et de Biologie Moléculaire et Cellulaire, University of York, Academic Medical Center
Pages: 1312-1319
Publication date: 2015
Peer-reviewed: Yes

Publication information
Journal: Prenatal Diagnosis
Volume: 34
Issue number: 13
ISSN (Print): 0197-3851
Ratings:
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 2.52 SJR 1.45 SNIP 1.054
Web of Science (2015): Impact factor 3.043
Web of Science (2015): Indexed yes
Original language: English
DOIs:
IRF8-dependent DCs Play a Key Role in the Regulation of CD8 T Cell Responses to Epithelial-derived Antigen in the Steady State but not in Inflammation

The intestinal immune system has the complex task of generating tolerance towards harmless antigens derived from our diet, commensal microflora or tissue, while maintaining the ability to mount protective immune responses to mucosal pathogens. Much of our understanding regarding the regulation of mucosal T cell responses stems from studies on CD4+ T cells. However, the intestinal mucosa is a major entry site for intracellular pathogens, whose control requires cross-presentation of cell-associated antigens for the induction of protective CD8+ T cell responses. To assess the regulation of mucosal CD8+ T cell priming and differentiation in the steady state and inflammatory setting, we utilized IFABP-tOva mice, in which Ovalbumin (Ova) is expressed as an epithelial-derived antigen in the small intestine. In this model Ova-specific CD8+ T cells were found to differentiate into two distinct subsets, CD107a/b+ cytotoxic T cells (CTLs) and FoxP3+ CD8+ T cells with regulatory potential. Interestingly, neither IRF8 nor IRF4 expression by intestinal dendritic cells (DCs) was crucial for the expansion of CTLs. In contrast, presence of IRF8- but not IRF4-dependent DCs was critical for the development of FoxP3+ CD8+ T cells in the steady state. However in the inflammatory setting, expansion of the FoxP3+ subset was not affected by the absence of IRF8-dependent DCs, suggesting that other subsets of intestinal antigen presenting cells (APCs) can compensate their function in an inflammatory milieu. Collectively these findings further our understanding of the mechanisms regulating CD8+ T cell responses in the intestinal mucosa and have potential implications for mucosal vaccine design.

Lymph-borne CD8α+ dendritic cells are uniquely able to cross-prime CD8+ T cells with antigen acquired from intestinal epithelial cells

Cross-presentation of cellular antigens is crucial for priming CD8+ T cells, and generating immunity to intracellular pathogens—particularly viruses. It is unclear which intestinal phagocytes perform this function in vivo. To address this, we examined dendritic cells (DCs) from the intestinal lymph of IFABP-tOVA 232-4 mice, which express ovalbumin in small intestinal epithelial cells (IECs). Among lymph DCs (LDCs) only CD103+ CD11b− CD8α+ DCs cross-present IEC-derived ovalbumin to CD8+ OT-I T cells. Similarly, in the mesenteric lymph nodes (MLNs), cross-presentation of IEC–ovalbumin was limited to the CD11c+ MHCIIhi CD8α+ migratory DCs, but absent from all other subsets, including the resident CD8αhi DCs. Crucially, delivery of purified CD8α+ LDCs, but not other LDC subsets, into the MLN subcapsular lymphatic sinus induced proliferation of ovalbumin-specific, gut-tropic CD8+ T cells in vivo. Finally, in 232-4 mice treated with R848, CD8α+ LDCs were uniquely able to cross-prime interferon γ-producing CD8+ T cells and drive their migration to the intestine. Our results clearly demonstrate that migrating CD8α+ intestinal DCs are indispensable for cross-presentation of cellular antigens and, in conditions of inflammation, for the initial differentiation of effector CD8+ T cells. They may therefore represent an important target for the development of antiviral vaccinations.
Lymphocyte Trafficking to Mucosal Tissues

Lymphocytes are the key cells of the adaptive immune system that provide antigen-specific responses tailored to the context of antigen exposure. Through cytokine release and antibody production, lymphocytes orchestrate and amplify the recruitment and function of other immune cells and contribute to host defense against invading pathogens and the pathogenesis of many inflammatory diseases. Lymphocyte function is critically dependent on their ability to traffic into the correct anatomic locations at the appropriate times. This process is highly regulated and requires that lymphocytes interact with various homing molecules and respond to tightly regulated navigational cues.

Bibliographical note
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Source: PublicationPreSubmission
Source-ID: 96613803
Research output: Contribution to journal › Journal article – Annual report year: 2015 › Research › peer-review

MyD88 Signaling Regulates Steady-State Migration of Intestinal CD103⁺ Dendritic Cells Independently of TNF-α and the Gut Microbiota

Intestinal homeostasis and induction of systemic tolerance to fed Ags (i.e., oral tolerance) rely on the steady-state migration of small intestinal lamina propria dendritic cells (DCs) into draining mesenteric lymph nodes (MLN). The majority of these migratory DCs express the α integrin chain CD103, and in this study we demonstrate that the steady-state mobilization of CD103⁺ DCs into the MLN is in part governed by the IL-1R family/TLR signaling adaptor molecule MyD88. Similar to mice with complete MyD88 deficiency, specific deletion of MyD88 in DCs resulted in a 50–60% reduction in short-term accumulation of both CD103⁺CD11b⁺ and CD103⁺CD11b⁻ DCs in the MLN. DC migration was independent of caspase-1, which is responsible for the inflammasomedependent proteolytic activation of IL-1 cytokine family members, and was not affected by treatment with broad-spectrum antibiotics. Consistent with the latter finding, the proportion and phenotypic composition of DCs were similar in mesenteric lymph from germ-free and conventionally housed mice. Although TNF-α was required for CD103⁺ DC migration to the MLN after oral administration of the TLR7 agonist R848, it was not required for the steady-state migration of these cells. Similarly, TLR signaling through the adaptor molecule Toll/IL-1R domain-containing adapter inducing IFN-β and downstream production of type I IFN were not required for steady-state CD103⁺ DC migration. Taken together, our results demonstrate that MyD88 signaling in DCs, independently of the microbiota and TNF-α, is required for optimal steady-state migration of small intestinal lamina propria CD103⁺ DCs into the MLN.
Physiological Role of TNF in Mucosal Immunology: Regulation of Macrophage/Dendritic Cell Function

Intestinal mononuclear phagocytes, comprising macrophages (Mφs) and dendritic cells (DCs), play important roles in the generation and the regulation of immune responses to intestinal antigens, and alterations in the development and/or the function of these cells are thought to contribute to the pathogenesis of inflammatory bowel disease. In this review, we discuss the role of tumor necrosis factor-α (TNF) in regulating multiple aspects of intestinal Mφ and DC physiology, including their differentiation, migration, maturation, survival and effector functions. In inflammatory bowel disease, TNF signaling has been implicated in reprogramming monocyte differentiation from the anti-inflammatory Mφ lineage towards the pro-inflammatory mononuclear phagocyte lineage. These cells become a major source of TNF and, thus, may contribute to the chronic inflammatory process. Finally, we highlight some of the important gaps in our current knowledge regarding the role of TNF in Mφ and DC physiology and suggest important directions for future research in this field.

Retinoic acid signalling in thymocytes regulates T cell development

The Vitamin A derivative retinoic acid (RA) has emerged as an important regulator of peripheral T cell responses. However, whether there is endogenous retinoic acid receptor (RAR) signaling in developing thymocytes and the potential impact of such signals in thymocyte development remains unclear. Here, using a RA sensitive reporter mouse model, we demonstrate that endogenous RAR responses are induced in CD69<sup>+</sup>CD4<sup>+</sup>CD8<sup>+</sup> and CD69<sup>+</sup>CD4<sup>+</sup>CD8<sup>+</sup> thymocytes undergoing positive selection and lineage commitment, and continue to be present in both CD4<sup>+</sup> and CD8<sup>+</sup> single positive (SP) cells, with RA signaling further enhanced in recently generated CD69<sup>+</sup> CD4<sup>+</sup> SP cells. To address the potential
biological significance of RA signaling in developing thymocytes, we evaluated T cell development in CD4Cre-dnRAR mice, where RA signaling is blocked in thymocytes from the CD4+CD8+ double positive (DP) stage onwards due to expression of a dominant-negative form of RAR. Interestingly, these mice displayed a marked reduction in all thymocyte subsets, with the exception of CD8+ SP cells but including ETP and DN2-4 subsets, suggesting that blocked RA signaling in DP thymocytes and their progeny indirectly impacts on thymocyte precursor entry and/or survival. Furthermore, CD4Cre-dnRAR mice showed a 4-fold reduction in CD4+/CD8+ SP ratio that was mainly due to enhanced accumulation of mature CD8+ SP cells, indicating that RA signaling may be directly involved in regulating thymic retention and/or post-selection expansion of this cell subset. Collectively, our data suggest a direct role for RA signaling in regulating thymocyte homeostasis and T cell development.

Retinoic acid signalling is required for the efficient differentiation of CD4+ T cells into pathogenic effector cells during the development of intestinal inflammation

Epidemiological studies of vitamin A-deficient populations have illustrated the importance of the vitamin A metabolite retinoic acid (RA) in mucosal immune responses. However, RA seems to be a double-edge sword in CD4+ T cell biology. While it sustains the development of foxp3+ regulatory T cells, it was also very recently reported to be essential for the stability of the Th1 lineage and to prevent transition to a Th17 program. Here we explored the role of RA signalling in CD4+ T cells during the development of intestinal inflammation in the T cell transfer colitis model. We found that RA signalling-deficient CD4+ T cells are less potent at inducing intestinal inflammation compared to their RA signalling-competent counterparts and exhibit a differentiation skewing towards more IFNγ- IL-17+, IL-17+IFNγ+ and foxp3+ cells, while their capacity to differentiate into IL-17-IFNγ+ Th1 cells is compromised. In vitro studies confirm the inefficacy of RA signalling-deficient T cells to generate bona fide Th1 cells and demonstrate their aberrant increased RORγt expression while their differentiation into Th17 remains unaffected. Surprisingly, RA signalling-deficient CD45RBlo regulatory T cells (Tregs) are however as efficient as their RA signalling-competent counterparts to inhibit colitis development.

Together our results indicate that RA, through its receptor RARα, negatively regulates the early expansion of CD4+ T cells...
during colitis and is necessary for the generation of colitogenic Th1/Th17 cells, while it is dispensable for the protective function of Treg cells. We are currently deciphering the mechanisms of these effects of RA on CD4+ T cells.

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University
Contributors: Rivollier, A. M. C., Pool, L., Frising, U., Wendland, K., Agace, W. W.
Number of pages: 1
Publication date: 2015
Peer-reviewed: Yes
Event: Abstract from 17th International Congress of Mucosal Immunology, Berlin, Germany.
Electronic versions: 2015_04_15_AbstractICMI2015.pdf

Thymic and lymph node mesenchymal subsets can be derived from PDGFRα/β+Gp38+CD34+ICAM1- vascular adventitial precursors
While discrete Gp38- and Gp38+ mesenchymal populations have previously been described in the lymph nodes (LNs) and in the thymus the putative relationship between LN and thymic mesenchymal cells remains unclear. Here, using transcriptome profiling as well as phenotypic and localization studies we comprehensively assessed the mesenchymal cell subset composition of the LNs and the thymus. We find that while LNs selectively harbored a BP3+ PDGFRα+Gp38+ compartment consisting of CCL21-producing fibroblastic reticular cells (FRC), MAdCAM1+ marginal reticular cells (MRC) and CR1_2+ follicular dendritic cells (FDC), both organs were populated by two corresponding subsets of BP3+ PDGFRβ+ cells, PDGFRα-Gp38+ITGA7+ pericytes and PDGFRα+Gp38+CD34+ cells localized in the vascular adventitia and in the capsule. Focusing on the thymus as a model organ we obtain evidence that the latter two subsets initially developed from a common PDGFRα/β+Gp38+CD34+ICAM1- embryonic precursor population. Notably, precursor-progeny studies involving transfer of adult thymus- and adipose tissue-derived BP3+Gp38+PDGFRα+CD34+ICAM1- cells into thymic and LN re-aggregate organ grafts uncovered a precursor activity towards not only pericytes but also BP3+ FRC, MRC and FDC and provided evidence of local environmental imprinting of BP3+Gp38+ cells with organ-specific features. Finally, we demonstrate that BP3-Gp38+ mesenchymal cell maintenance/maturation in the thymus requires LTβR signaling while this pathway appeared dispensable for pericyte differentiation. These findings bring novel insights to the understanding of lymphoid mesenchymal cell heterogeneity and implicate an unforeseen role of the vascular adventitia in lymphoid stroma turnover/regeneration.

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University, University of Birmingham
Number of pages: 1
Publication date: 2015
Peer-reviewed: Yes
Event: Abstract from 1st International Venice Thymus Meeting, San Servolo Island, Italy.
Electronic versions: Katarzyna_Sitnik_abstract.docx
Research output: Contribution to conference › Conference abstract for conference – Annual report year: 2015 › Research › peer-review

CD14 hi HLA-DR dim macrophages, with a resemblance to classical blood monocytes, dominate inflamed mucosa in Crohn's disease
Intestinal MΦ play an important role in maintaining gut homeostasis. However, little is known about these cells, their precursors, and their role in intestinal inflammation. Here, we characterize the CD14 mononuclear cell populations in intestinal mucosa and blood in patients with CD. Among the LP CD14+ MΦ, we identified three distinct HLA-DR+ -expressing subsets. Compared with uninfamed, inflamed mucosa contained a marked increase in the proportion of CD14+HLA-DR+dim cellular subset. This subset resembled the classical bloodmonocytes with low CD16, HLA-DR, and CX3CR1 expression. Classical monocytes migrated efficiently towardCCL2 and released the highest levels of MMP-1 and proinflammatory cytokines when stimulated with immune complexes or LPS. Our findings strongly suggest that it is the classical and not the intermediate or nonclassical macrophages that are the precursors to the dominating intestinal CD14hi...
HLA-DRdim subset. This enhances our understanding of CD pathology and may provide new options in treatment.

General information
Publication status: Published
Organisations: Lund University, Hannover Medical School, Novo Nordisk AS
Pages: 531-541
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: Journal of Leukocyte Biology
Volume: 95
Issue number: 3
ISSN (Print): 0741-5400
Ratings:
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 3.94 SJR 2.525 SNIP 1.157
Web of Science (2014): Impact factor 4.289
Web of Science (2014): Indexed yes
Original language: English
DOIs:
10.1189/jlb.0113021
Source: PublicationPreSubmission
Source-ID: 96613811
Research output: Contribution to journal › Journal article – Annual report year: 2015 › Research › peer-review

Dendritic cell subsets in mucosal immune responses

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University
Contributors: Agace, W. W.
Number of pages: 1
Pages: 21
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: Immunology
Volume: 143
Issue number: SI
Article number: 148
ISSN (Print): 0019-2805
Ratings:
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 3.61 SJR 1.984 SNIP 1.029
Web of Science (2014): Impact factor 3.795
Web of Science (2014): Indexed yes
Original language: English

Bibliographical note
Special Issue - Supplement 2
Research output: Contribution to journal › Conference abstract in journal – Annual report year: 2015 › Research › peer-review

Dendritic cell subsets in the regulation of intestinal immune responses

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Ghent University, Lund University
Contributors: Luda, K., Persson, E., Joeris, T., Lambrecht, B., Agace, W. W.
Intestinal dendritic cells in the regulation of mucosal immunity.

The intestine presents a huge surface area to the outside environment, a property that is of critical importance for its key functions in nutrient digestion, absorption, and waste disposal. As such, the intestine is constantly exposed to dietary and microbial-derived foreign antigens, to which immune cells within the mucosa must suitably respond to maintain intestinal integrity, while also providing the ability to mount effective immune responses to potential pathogens. Dendritic cells (DCs) are sentinel immune cells that play a central role in the initiation and differentiation of adaptive immune responses. In the intestinal mucosa, DCs are located diffusely throughout the intestinal lamina propria, within gut-associated lymphoid tissues, including Peyer's patches and smaller lymphoid aggregates, as well as in intestinal-draining lymph nodes, including mesenteric lymph nodes. The recognition that dietary nutrients and microbial communities in the intestine influence both mucosal and systemic immune cell development and function as well as immune-mediated disease has led to an explosion of literature in mucosal immunology in recent years and a growing interest in the functionality of intestinal DCs. In the current review, we discuss recent findings from our group and others that have provided important insights regarding murine and human intestinal lamina propria DCs and highlighted marked developmental and functional heterogeneity within this compartment. A thorough understanding of the role these subsets play in the regulation of intestinal immune homeostasis and inflammation will help to define novel strategies for the treatment of intestinal pathologies and contribute to improved rational design of mucosal vaccines.
IRF4-Dependent Dendritic Cells Regulate CD4(+) T Cell Responses to Soluble Oral Antigens

General information
Publication status: Published
Organisations: Lund University, University of Glasgow
Contributors: Persson, E., Luda, K., Mowat, A., Kotarsky, K., Agace, W. W.
Number of pages: 1
Pages: 447
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: Scandinavian Journal of Immunology
Volume: 79
Issue number: 6
ISSN (Print): 0300-9475
Ratings:
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 1.91 SJR 0.869 SNIP 0.665
Web of Science (2014): Impact factor 1.739
Web of Science (2014): Indexed yes
Original language: English
Research output: Contribution to journal > Conference abstract in journal – Annual report year: 2015 > Research > peer-review

IRF4-dependent gut dendritic cells control the mucosal IgA response to flagellin

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University, University of Birmingham
Number of pages: 1
Pages: 59
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: Immunology
Volume: 143
Issue number: SI
Article number: 247
ISSN (Print): 0019-2805
Ratings:
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 3.61 SJR 1.984 SNIP 1.029
Web of Science (2014): Impact factor 3.795
Web of Science (2014): Indexed yes
Original language: English

Bibliographical note
Special Issue - Supplement 2
Research output: Contribution to journal > Conference abstract in journal – Annual report year: 2015 > Research > peer-review

Lymph-borne CD8 alpha+ dendritic cells are uniquely able to cross-prime CD8+ T cells with antigen acquired from intestinal epithelial cells

General information
Publication status: Published
Organisations: University of Glasgow, Ghent University, Lund University, Robert Koch Institute, University of Gothenburg
Regional specialization within the intestinal immune system.

The intestine represents the largest compartment of the immune system. It is continually exposed to antigens and immunomodulatory agents from the diet and the commensal microbiota, and it is the port of entry for many clinically important pathogens. Intestinal immune processes are also increasingly implicated in controlling disease development elsewhere in the body. In this Review, we detail the anatomical and physiological distinctions that are observed in the small and large intestines, and we suggest how these may account for the diversity in the immune apparatus that is seen throughout the intestine. We describe how the distribution of innate, adaptive and innate-like immune cells varies in different segments of the intestine and discuss the environmental factors that may influence this. Finally, we consider the implications of regional immune specialization for inflammatory disease in the intestine.

General information

Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, University of Glasgow
Contributors: Mowat, A. M., Agace, W. W.
Number of pages: 19
Pages: 667-685
Publication date: 2014
Peer-reviewed: Yes

Publication information

Journal: Nature Reviews. Immunology
Volume: 14
Issue number: 10
ISSN (Print): 1474-1733
Ratings:
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 15.03 SJR 26.955 SNIP 8.239
Web of Science (2014): Impact factor 34.985
Web of Science (2014): Indexed yes
Original language: English
DOIs:
10.1038/nri3738
Source: FindIt
Source-ID: 271180755
Research output: Contribution to journal › Journal article – Annual report year: 2014 › Research › peer-review

Requirement for IRF4-Dependent DCs for the Generation of Th2 Responses During Infection with the Murine Gastrointestinal Nematode Trichuris muris

General information
Retinoic acid modulates the early expansion and differentiation of CD4(+) T cells during the development of intestinal inflammation

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University
Contributors: Demiri, M., Persson, E., Agace, W. W., Svensson-Frej, M.
Number of pages: 1
Pages: 444
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: Scandinavian Journal of Immunology
Volume: 79
Issue number: 6
ISSN (Print): 0300-9475
Ratings:
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 1.91 SJR 0.869 SNIP 0.665
Web of Science (2014): Impact factor 1.739
Web of Science (2014): Indexed yes
Original language: English
Research output: Contribution to journal › Conference abstract in journal – Annual report year: 2015 › Research › peer-review

Retinoic Acid Modulates the Early Expansion and Differentiation of CD4(+) T Cells During the Development of Intestinal Inflammation

General information
Publication status: Published
Organisations: National Veterinary Institute, Section for Immunology and Vaccinology, Lund University
Contributors: Rivollier, A. M. C., Pool, L., Frising, U., Agace, W. W.
Number of pages: 1
Pages: 440-440
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: SCANDINAVIAN JOURNAL OF IMMUNOLOGY
Volume: 79
Role of Intestinal IRF8-Dependent CD103(+)CD11b(-) DCs in Intestinal Immune Homeostasis

**General information**

Publication status: Published
Organisations: Lund University
Contributors: Luda, K., Persson, E., Agace, W. W.
Number of pages: 1
Pages: 448
Publication date: 2014
Peer-reviewed: Yes

**Publication information**

Journal: Scandinavian Journal of Immunology
Volume: 79
Issue number: 6
ISSN (Print): 0300-9475
Ratings:
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 1.91 SJR 0.869 SNIP 0.665
Web of Science (2014): Impact factor 1.739
Web of Science (2014): Indexed yes
Original language: English
Research output: Contribution to journal › Conference abstract in journal – Annual report year: 2015 › Research › peer-review

Dendritic cell subsets in the intestinal lamina propria: Ontogeny and function

The intestinal mucosa is exposed to large amounts of foreign antigen (Ag) derived from commensal bacteria, dietary Ags, and intestinal pathogens. Dendritic cells (DCs) are believed to be involved in the induction of tolerance to harmless Ags and in mounting protective immune responses to pathogens and, as such, to play key roles in regulating intestinal immune homeostasis. The characterization of classical DCs (cDCs) in the intestinal lamina propria has been under intense investigation in recent years but the use of markers (including CD11c, CD11b, MHC class II), which are also expressed by intestinal M phi s, has led to some controversy regarding their definition. Here we review recent studies that help to distinguish cDCs subsets from monocyte-derived cells in the intestinal mucosa. We address the phenotype and ontogeny of these cDC subsets and highlight recent findings indicating that these subsets play distinct roles in the regulation of mucosal immune responses in vivo.

**General information**

Publication status: Published
Organisations: Lund University, University of Glasgow, University of Copenhagen
Number of pages: 10
Pages: 3098-3107
Publication date: 2013
Peer-reviewed: Yes

**Publication information**

Journal: European Journal of Immunology
Volume: 43
Eosinophils Are Crucial for Mediating the Anticontractile Capacity of Perivascular Adipose Tissue

General information
Publication status: Published
Organisations: Lund University, University of Manchester
Contributors: Withers, S., Forman, R., Else, K., Meza-Perez, S., Agace, W. W., Cruickshank, S., Heagerty, A., Svensson-Frej, M.
Publication date: 2013
Peer-reviewed: Yes

Publication information
Journal: Circulation
Volume: 128
Issue number: 22
Article number: 17594
ISSN (Print): 0009-7322
Ratings:
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 9.32
Web of Science (2013): Impact factor 11.089
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
Original language: English
Research output: Contribution to journal – Conference abstract in journal – Annual report year: 2013 – Research – peer-review

IRF4 Transcription-Factor-Dependent CD103(+)CD11b(+) Dendritic Cells Drive Mucosal T Helper 17 Cell Differentiation

CD103(+)CD11b(+) dendritic cells (DCs) represent the major migratory DC population within the small intestinal lamina propria (SI-LP), but their in vivo function remains unclear. Here we demonstrate that intestinal CD103(+)CD11b(+) DC survival was dependent on interferon regulatory factor 4 (IRF4). Mice with a DC deletion in Irf4 displayed reduced numbers of intestinal interleukin 17 (IL-17)-secreting helper T 17 (Th17) cells and failed to support Th17 cell differentiation in draining mesenteric lymph nodes (MLN) following immunization. The latter was associated with a selective reduction in CD103(+)CD11b(+) MLN DCs and DC derived IL-6. Immunized I6(-/-) mice failed to support Th17 cell differentiation in MLN in vivo and CD103(+)CD11b(+) MLN DCs supported IL-6-dependent Th17 cell differentiation in vitro. Together, our results suggest a central role for IRF4-dependent, IL-6 producing CD103(+)CD11b(+) DCs in intestinal Th17 cell differentiation.

General information
Publication status: Published
Organisations: Lund University, Skåne University Hospital, Columbia University, University of Copenhagen
Number of pages: 12
Pages: 958-969
Publication date: 2013
Lymph borne CD8 alpha(+) DCs are uniquely able to cross-prime CD8(+) T cells with antigen acquired from intestinal epithelial cells

The role of eosinophils in perivascular adipose tissue
Lymphocyte Trafficking from Inductive Sites to Effector Sites

The initiation, maintenance, and resolution of innate and adaptive immune responses are critically dependent on immune cell migration, not only within tissues but often over long distances between organs. This process is highly dynamic and requires that immune cells interact with multiple vascular, lymphatic, and tissue environments in a tightly controlled and organized fashion. Most infections will initially constitute a small number of pathogens and be localized to a small tissue area. If naive lymphocytes were tissue-resident cells dispersed at random throughout the body, the chances that a given antigen specific lymphocyte would be at the right site—that is, at the site of pathogen entry—would be very slim. In a rough calculation, we might estimate that a T lymphocyte with a diameter of 10 μm and a volume of about $0.5 \times 10^{-18} \text{m}^3$ occupies less than 10−15% of the body volume. Even if we suppose that several hundred T lymphocytes recognize a distinct antigen, the odds of an antigen-specific lymphocyte’s being in the same location as a pathogen remain extremely low. Lymphocyte recirculation solves this problem by enabling the entire T lymphocyte population to scan antigen-presenting cells within lymphoid compartments. Perhaps nowhere is this more obvious than during the induction of adaptive immune responses. Adaptive immunity is initiated when antigen-presenting cells, primarily dendritic cells (DCs), present antigen to lymphocytes in inductive immune compartments, such as lymph nodes and Peyer’s patches. During mucosal immune responses, antigen-bearing DCs migrate from mucosal tissues through draining afferent lymph vessels to regional lymph nodes and into the lymph node T-cell zone. Conversely, to find a DC presenting relevant cognate antigen: major histocompatibility complex (MHC), naive lymphocytes continually traffic from the bloodstream into lymph nodes and back via efferent lymph to the venous blood. In combination, these migratory routes of DCs and lymphocytes allow frequent contact of both cell types and thus form the basis for the efficient induction of adaptive immune responses. Besides the constitutive recirculation of naive lymphocytes, immune cells need to be directed to sites of inflammation. This holds true for cells of the innate immune system, including monocytes and granulocytes, which are rapidly recruited to the inflamed tissue during the initial phase of an immunoreaction, and also for effector T cells and plasma cells, which are generated in the adaptive immune response.

Resident and pro-inflammatory macrophages in the colon represent alternative context dependent fates of the same Ly6Chi monocyte precursors

Macrophages (mφ) are essential for intestinal homeostasis and the pathology of inflammatory bowel disease (IBD), but it is unclear whether discrete mφ populations carry out these distinct functions or if resident mφ change during inflammation. We show here that most resident mφ in resting mouse colon express very high levels of CX3CR1, are avidly phagocytic and MHCIIhi, but are resistant to Toll-like receptor (TLR) stimulation, produce interleukin 10 constitutively, and express CD163 and CD206. A smaller population of CX3CR1int cells is present in resting colon and it expands during experimental colitis. Ly6CintCCR2+ monocytes can give rise to all mφ subsets in both healthy and inflamed colon and we show that the CX3CR1int pool represents a continuum in which newly arrived, recently divided monocytes develop into resident CX3CR1hi mφ. This process is arrested during experimental colitis, resulting in the accumulation of TLR-responsive pro-inflammatory mφ. Phenotypic analysis of human intestinal mφ indicates that analogous processes occur in the normal and Crohn’s disease ileum. These studies show for the first time that resident and inflammatory mφ in the intestine represent alternative differentiation outcomes of the same precursor and targeting these events could offer routes...
for therapeutic intervention in IBD.

**General information**
Publication status: Published
Organisations: Lund University
Contributors: Bain, C. C., Scott, C. L., Uronen-Hansson, H., Gudjonsson, S., Jansson, O., Grip, O., Guilliams, M., Malissen, B., Agace, W. W., Mowat, A. M.
Pages: 498-510
Publication date: 2012
Peer-reviewed: Yes

**Publication information**
Journal: Mucosal Immunology
Volume: 6
Issue number: 3
ISSN (Print): 1933-0219
Ratings:
Scopus rating (2012): CiteScore 6.69 SJR 3.895 SNIP 1.643
Web of Science (2012): Impact factor 7
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Original language: English
Electronic versions:

**mi201289a.pdf**
**DOI:** 10.1038/mi.2012.89
Source: FindIt
Source-ID: 2315886868
Research output: Contribution to journal › Journal article – Annual report year: 2012 › Research › peer-review