Intestinal Antigen Presenting Cells and Antigen Delivery

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Some additional reading material (reviews)

**Mucosal antigen presenting cell subsets**


**Antigen delivery across the mucosa**

Overview of Talk

1. Overview of intestinal DC subsets
2. How do DCs acquire antigen from the lumen
3. Function of DC subsets in intestinal homeostasis
The intestinal environment represents a unique challenge to our immune system.

Tolerance

Immunity

Inflammatory Bowel disease (Crohn’s, Ulcerative Colitis), celiac disease
Adaptive immune cells in the intestinal mucosa

Physiological inflammation = presence of a large number of activated leukocytes in the normal (steady-state) intestine
Dendritic cells provide a key link between the innate and adaptive immune responses

- Derive from committed precursors in BM
- Enter as immature precursors (pre DC) into all tissue of body
  - Tissue derived migratory DCs
  - LN resident DCs
- Short lived (days)
1. Overview of intestinal DC subsets
cDCs reside throughout the intestinal mucosa

In steady state, migratory DCs in LN can be identified by their high expression of MHCII
Dendritic cell subsets in the intestinal mucosa
Gating strategy to identify cDC subsets in the murine intestinal LP

A. Live CD45+ siLP cells

B. CD11c vs. MHC II

C. CD11c vs. CD64

D. CD103 vs. CD11b

E. CD103 vs. CD11b

F. Xcr1+ and Sirpα+ cells
Schulz et al, JEM 2009
Cerovic et al, MI 2013

- CD103+CD11b+
- CD103+CD11b-
- CD103- DCs

No CD64+ cells (macrophages)
Equivalent DC subsets in the human intestine

Persson et al, Immunity 2013
Watchmaker et al, Nat. Imm. 2014

Bekiaris et al, Immun Rev 2014
2. How do DCs acquire antigen from the lumen?
Microfold cells (M cells)

- Not covered by glycocalyx
- Do not secrete mucous
- No microvilli
- Specialized in particulate antigen uptake
- Utilized by pathogenic bacteria/viruses to gain entry into host
Antigen uptake into the intestinal lamina propria
Intestinal macrophages sample the intestinal lumen and have been suggested to pass antigen to neighboring DCs. 

Oral tolerance can be established via gap junction transfer of fed antigens from CX3CR1⁺ macrophages to CD103⁺ dendritic cells. 

Mazzini E¹, Massimiliano L¹, Penna G¹, Rescigno M². Immunity. 2014 Feb 20;40(2):248-61
DCs can acquire luminal antigen via goblet associated antigen passages (GAPs)

McDole JR et al. Nature 2012

Beads: 0.02-1µm did not enter 10-70 kDa proteins could enter
Intestinal dendritic cells migrate through the intestinal epithelium and can directly capture particulate as well as soluble antigen.

Farache J et al, Immunity 2013
Multiple mechanisms of luminal antigen uptake:

- Transcellular diffusion (endocytosis and exocytosis)
- Uptake by Lysozyme M+ DCs in FAE. Lelouard et al. Gastroenterology 2012.
3. Function of DC subsets in intestinal homeostasis

Intestinal DC functionality is determined by their ontogeny (ie cDC1 and cDC2 subsets appear to have unique functionalities independent of which tissue they sit in)

BUT

their function is also regulated by local environmental queues
Murine small intestinal DCs display an enhanced ability to generate the Vitamin A metabolite, retinoic acid

**RA functionalities (selected)**

- Induction of gut homing receptors CCR9 and α4β7
- Synergizes with TGFβ to promote iTreg induction
- Promotes IgA switching in B cells
- Required for Th1 differentiation

Short talk: Wed 19th

Retinoic acid signaling is required for the pathogenicity of effector CD4+ T cells during the development of intestinal inflammation. Rivollier. Poster W81
Role of cDC1 in intestinal immune homeostasis in vivo

Models
- Batf3^-/
- Cd11c-cre.Irf8^fl/fl
- Zbtb46-cre.Irf8^fl/fl
- XCR1-cre.Irf8^fl/fl
- Xcr1-DTA
- Clec9a-DTR
cDC1 are required for intestinal Th1 cell homeostasis

Luda et al, Immunity 2016
cDC1 are required for IEL homeostasis
Role of cDC1 in intestinal T cell homeostasis
Role of cDC2 play in intestinal immune homeostasis in vivo

Models

\( Cd11c-cre.Klf4^{fl/fl} \)
\( Clec4a4\text{-DTR} \)
\( Sirpa^{-/-} \)
\( huLangerin\text{-DTA} \)
\( Cd11c-cre.Irf4^{fl/fl} \)
\( Cd11c-cre.Notch2^{fl/fl} \)
CD11cCre.IRF4^{fl/fl} mice have reduced numbers of Th17 cells in the intestinal mucosa

Persson et al., Immunity 2013
cDC2 are required for Th_{17} differentiation in MLN
Different populations of CD11b+ dendritic cells drive Th2 responses in the small intestine and colon. Mayer JU\textsuperscript{1}, Demiri M\textsuperscript{2}, Agace WW\textsuperscript{2,3}, MacDonald AS\textsuperscript{4}, Svensson-Frej M\textsuperscript{2}, Milling SW\textsuperscript{1}.

Control of T helper 2 responses by transcription factor IRF4-dependent dendritic cells. Gao Y\textsuperscript{1}, Nish SA, Jiang R, Hou L, Licona-Limón P, Weinstein JS, Zhao H, Medzhitov R.

Klf4 expression in conventional dendritic cells is required for T helper 2 cell responses. Tussiwand R\textsuperscript{1}, Everts B\textsuperscript{2}, Grajales-Reyes GE\textsuperscript{3}, Kretzer NM\textsuperscript{3}, Iwata A\textsuperscript{3}, Bagaitkar J\textsuperscript{4}, Wu X\textsuperscript{3}, Wong R\textsuperscript{3}, Anderson DA\textsuperscript{3}, Murphy TL\textsuperscript{3}, Pearce EJ\textsuperscript{3}, Murphy KM\textsuperscript{5}.

cDC2 are required for mucosal Th2 responses
**Intestinal DC subsets have distinct roles in mucosal immune homeostasis**

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<thead>
<tr>
<th>Phenotype</th>
<th>Ontogeny</th>
<th>Function</th>
<th>Abundance</th>
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<tbody>
<tr>
<td>cDC1</td>
<td>XCR1⁺</td>
<td>Th1</td>
<td>++</td>
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<tr>
<td></td>
<td>CD11c⁺</td>
<td>Cross presentation</td>
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<td>MHC II⁺</td>
<td>Induction of CD8αβ⁺ and CTL-like CD8αβ⁺ CD4⁺ IEL</td>
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<td>CD11b⁻</td>
<td>Predominant in CCR9/α,β, induction</td>
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<td></td>
<td>CX3CR1⁻</td>
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<tr>
<td>cDC2</td>
<td>IRF4⁺</td>
<td>Th17</td>
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<td>KLF4⁺</td>
<td>Th2</td>
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<td></td>
<td>Notch2⁺</td>
<td>ILC3 activation</td>
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<td>ZBTB46</td>
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**cDC1**
Luda et al, Immunity 2016
Cerovic et al, M.I 2015

**cDC2**
Persson et al, Immunity 2013
Lewis et al, Immunity 2011
Welty et al, J.E.M 2013
Schlitzer et al, Immunity 2013
Gao et al, Immunity 2013
Mayer et al, Nature Comm 2017
Scott et al, M.I 2015
Take home messages

• Mucosal tissues contain a complex network of DC subsets

• DC subsets play distinct non-redundant roles in the regulation of mucosal adaptive immune responses

• DC functionality is determined by cell intrinsic properties acquired during their development

• AND by signals they receive in their local environment
Some short talks/posters regarding intestinal DC subset functionality (my group)

IRF8-Dependent DCs Play a Key Role in the Maintenance of CD8 T Cell Tolerance to Epithelial-Derived Antigen. **Thorsten Joeris**
Wednesday, July 19th: 4:15:00 PM Session Name: Dendritic Cells **OR.24, W16.**

Delayed onset of T cell transfer colitis in the absence of IRF4 dependent DCs. **Lieneke Poole.** Wed 19th **W10**