Control of intestinal inflammation by regulatory T cells

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Regulatory T cells prevent immune pathology in the intestine

1. Mechanisms of $T_R$ mediated suppression of colitis
2. Identification of the gut as a site of $T_R$ generation-role of specialised DC
1. Naturally occurring T_R (CD4^+CD25^+Foxp3^+)

   Foxp3 necessary for development and function
   Mutations in Foxp3 gene cause lethal multi-organ inflammatory condition

   Suppress response to self & foreign Ag:
   - Autoimmunity
   - Immunity to infection
   - Allergy
   - Tumour immunity
   - IBD
   - Transplant rejection

2. Adaptive/Induced T_R

   IL-10, TGF-b, Foxp3
Prevention of colitis involves IL-10, TGF-beta and CTLA4

TR cells prevent accumulation of activated DC

Directly suppress the innate response via IL-10 production

Powrie et al., JEM 1994, Read et al., JEM 2001, Maloy et al., JEM 2003
$T_R$ cells cure colitis

TR cells cure established colitis. Proliferate in MLN and colon in close contact with $T_E$ and DC

Dependent on IL-10

Uhlig et al., JI, 2006; Mottet et al., JI 2003
Regulatory T cells in the intestine produce IL-10

Uhlig et al., JI, 2006
Ag exposure in the gut induces tolerance

- Apoptotic IEL
- Luminal Ag
- Constitutive Migration
- Gut Homing
- IL-10
Oral administration of ovalbumin induces Foxp3$^+$ T cells from naïve precursors

OVA

BSA

DO11.10 SCID

MLN, Spleen, Colon LP

5d

CD4

Foxp3

OVA

1.30

BSA

0.14
CD103 a marker of gut DC

- αE integrin subunit
- Expressed by mucosal DC and T Cells
- Pairs with β7, binds to E-cadherin on epithelial cells

Annacker et al., JEM 2005, Lindbom et al., 2005
# Functional properties of CD103+ DC

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<tr>
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<th>CD103⁺</th>
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<tr>
<td>Naïve T cell Proliferation</td>
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<td>IFN-gamma</td>
<td>-</td>
<td>+</td>
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<td>Inflammatory Cytokines (IL-6, IL-23)</td>
<td>-</td>
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<td>Imprint gut homing Receptors</td>
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CD103 expression in RAG-/- required for TR activity

*Annacker et al., JEM 2005; Coombes et al., JEM 2007*
Sorting DC for *in vitro* T cell differentiation assay

Balb/c

MLN

CD11c MACS

CD103+ and CD103- subsets sorted on MoFlo

CD103

CD11c

CD103+

CD103-

CFSE Naïve
D011.10/SCID CD4+ T

+ OVAp

analysis

d4

IL-2

d7

αCD3

d8

analysis

cytokines
CD103+ DC promote the expression of Foxp3 by naïve T cells.
Induction of Foxp3 by CD103+ DC is TGF-β dependent

TGF-β-mediated induction of Foxp3 is increased in the presence of CD103+DC

Induction of Foxp3 by CD103+ DC is TGF-β dependent
CD103+ DCs express higher levels of retinal dehydrogenase than CD103- DCs

Cellular Retinoid Metabolism

- **Retinol (Vitamin A)**
  - ADHs
  - SDR

- **Retinal**
  - ALDH1A1
  - ALDH1A2
  - ALDH1A3

- **Retinoic Acid**

Mucosal epithelial cells and CD11c+ DCs in the dome areas of the small intestine express ALDH1A1, whilst MLN-DCs express ALDH1A2 (Iwata et al., Immunity, 2004)
Retinoic acid acts as a co-factor for Foxp3 induction

Spontaneous induction of Foxp3 in the presence of CD103+ DC is inhibited by an RAR antagonist
Foxp3+ cells suppress T cell proliferation in vitro (Yasmine Belkaid, Jason Hall)
Coombes et al., 2007; Hall et al., 2007; Benson et al. 2007; Murcida et al 2007
Summary

- Natural $T_R$ cells respond to inflammation and cure established colitis

- Compartmentalisation of the $T_R$ response-key role of IL-10 in control of tissue inflammation

- Gut is a site that favours induction of Foxp3+$T_R$ cells

- GALT contains functionally specialised CD103$^+$ DC

- CD103$^+$ DC imprint gut homing receptors on T cells and induce FoxP3 expression by a TGF-$\beta$ and RA dependent mechanism

- A mechanism to broaden the repertoire of $T_R$ cells responding to intestinal antigens

- In addition to natural $T_R$ cells, induced $T_R$ may play an important role in intestinal homeostasis
CD103+ DC: mucosal DC that support the development of Foxp3+ T<sub>R</sub> cells with a mucosal seeking phenotype
Complimentary therapies for intestinal inflammation?

Dysregulated responses

TNF-α

IL-6

IFN-γ

IL-17

IL-23

IL-10

TGF-β

T_R activity

Ab blockade

DC

Tn

M

N

N

Th1

Th1

Th1

Foxp3+

Treg
SWDSP:

Chris Mottet
Holm Uhlig
Oliver Annacker
Ana Izcue
Janine Coombes
Sophie Hue
Sophia Buonocore
Karima Siddiqui
Kevin Maloy

NIH
Yasmine Belkaid
Jason Hall

Wellcome Trust
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