Intestinal homeostasis and its breakdown in IBD

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Fondation Merieux
10/6/13
Maladaptations between the intestinal microbiota and innate and adaptive immune response promote IBD

- Microbiota changes
- Intestinal barrier function
- Anti-microbial defense
- Balance between effector and regulatory T cell responses

Adapted from Xavier Nature 2011
Deficiencies in *H. hepaticus*-induced IL-10 leads to IL-23-mediated colitis

Kullberg et al., JEM 2003; Hue et al., JEM 2006

IL-23 dependent colitis
IL-17-independent
The IL-23/Th17 Pathway-distinct mediators may promote particular tissue responses.

**Host defence**
- AMP’s
- Barrier function, repair

**Inflammation**
- GWAS: AS, CD, UC, Psoriasis
- Models: colitis, joint, skin, uveitis, CNS

**Naïve T-cell**
- IL-1, IL-6
- TGF-β, IL-23

**Th17 cell**
- (CD8, unconv T cells, ILC)
- IL-21
- IFN-γ
- TNF-α

**IL23R**
- RORgt
- IL-23
- IL-22
- IL-17A
- IL-17F
- GM-CSF

**Myeloid Cells**
- APCs

**Stromal Cells**
- Inflammation

**Barrier function, repair**
IL-23 acts directly on T cells to promote colitis

Ahern et al., Immunity 2010
Colitis is characterised by high numbers of mature and myeloid progenitor cells—role of GM-CSF?

Colonic CD4+

Colonic CD4+ T cells Griseri et al., Immunity 2012

Marginal CFU activity in the colon ~10X increased during colitis

control
colitis

N° colonic GMP

GM-CSF

IL-17A

CD4+ CD45RBhi

RAG-/-

GR1

CD11b

IL-17A

CFU-GM

control
colitic

Marginal CFU activity in the colon ~10X increased during colitis

T Griseri et al., Immunity 2012
GM-CSF promotes chronic intestinal inflammation

**colitis**

![Graph showing relationship between treatment and colitis](image)

\[ p=0.009 \]

**colonic neutrophils**

\[ \text{N}^0 \text{ CD11b}^+ \text{Gr}1^{hi} \text{ cells} \]

\[ p=0.05 \]

\[ (x10^4 \text{ cells}) \]

**GMP**

\[ \text{N}^0 \text{ GMP} \]

\[ p=0.02 \]

\[ (x10^3 \text{ cells}) \]

\[ \text{RB}^{hi} + \text{isotype control} \]

\[ \text{RB}^{hi} + \text{anti-GM-CSF} \]

Griseri et al., Immunity 2012
Eosinophils and the gastrointestinal tract

- Eosinophils are abundant throughout the GI tract
- Present in germ free mice
- Contributors to the immune response
- Can mediate tissue damage
- Increased in acute colitis
- Increased activation in IBD

Rosenberg HF Nat Rev Imm 2013
GM-CSF promotes dysregulated myelopoiesis: Colitogenic role for tissue toxic eosinophils

Stem cells

HSC

IFN-γ

GM-CSF

BONE MARROW

CLP

MEP

CLP

MEP

EMH

GMP

GMP

Eosinophils

IL-23

Th1/Th17

IFN-γ

IL-17

GM-CSF

Neutrophils

Inflammatory monocytes

microbiota

damage

Lamina propria

Blood

Haematopoiesis

Chronic Intestinal Inflammation
IL-23-driven innate colitis—genetically controlled response to Hh with hallmarks of type 17 response

Helicobacter hepaticus: innate model

129SvEv RAG⁻/⁻

H. hep

Colitis and colon cancer in 129SvEv C57Bl6 resistant (mapped to Chr3)

α-IL-23
α-IL-17A
α-IFNγ

Histopathology Score

Hue et al., JEM 2006; Buonocore et al., Nature 2010; Boulard JEM 2012; Szabady unpublished
**IL23-responsive innate lymphoid cells**

- IL23 induces Th17/Th1 cytokines by a novel population of innate lymphoid cells

Buonocore et al., *Nature* 2010
IL-23 drives innate colitis through promoting IFN-\(\gamma\) and IL-17 by innate lymphoid cells

INFLAMMATION

Innate cell involved in the tissue inflammatory response

Respond to early microbially-induced IL-23

ROR\(\gamma\)t-dependent cytokine module

May be involved in early amplification of the inflammatory response

Increased Type 17 ILC in CD lesions (Geremia et al., JEM 2011)
Type 3 ILC

Required for lymphoid organogenesis
Dependent on RORγt

Lti-like cells produce IL-17 and IL-22 in response to IL-23-host protective in CR infection

IL-22 producing ILC
Bears NK markers
Mediates anti-microbial immunity in intestine

IL-17, IL-22 and IFN-gamma producing ILC
Promote intestinal inflammation

H. Hepaticus-induced invasive colorectal cancer

*Helicobacter hepaticus*: innate model

129SvEv
RAG<sup>−/−</sup>

H. hep

6 w AOM

5 m analysis

**Highest tumor grade**

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<th>Grade</th>
<th>Percentage</th>
<th>Count</th>
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<tbody>
<tr>
<td>No CRC</td>
<td>0%</td>
<td></td>
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<tr>
<td>Low-grade dysplasia</td>
<td>75%</td>
<td>(n=12)</td>
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<tr>
<td>High-grade dysplasia</td>
<td>6%</td>
<td>(n=1)</td>
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<tr>
<td>CRC</td>
<td>19%</td>
<td>(n=3)</td>
</tr>
<tr>
<td>CRC</td>
<td>64%</td>
<td>(n=9)</td>
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129 CRC
C3B normal

Boulard et al., JEM 2012
Changes in the ILC compartment during *H. hepaticus* induced cancer

*Hh*+AOM

E-cadherin  RORγ  DAPI  IL-7Rα  DAPI

ILC composition

<table>
<thead>
<tr>
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<th>cILC</th>
<th>Nkp46⁺</th>
<th>LTI</th>
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ILC number

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Anti-Thy-1 tx reverses established inflammation and cancerous changes.
IL-22 as a pro-tumorigenic factor?

- Survival and growth factor produced by Th22, Nk-22, ILC, LTi
- **IL-22R** expression restricted to epithelium
- Signals through **Stat3**, which is involved in other CAC models
- **Polymorphisms in IL-22** associated with a 1.46-fold increased risk for development of CRC (Thompson et al. *Cancer Causes Control* 2010)
ILC produced IL-22 is acting on the epithelium to promote proliferation

1-3d 6-10w 20w

\[ \text{ILC produced IL-22 is acting on the epithelium to promote proliferation} \]

\[ \frac{1}{3} + \frac{1}{6} - 10w \]

\[ \text{CRC} \quad \text{Ab tx} \]

\[ \frac{Hh}{AOM} \]

\[ \text{Hh} + \text{AOM} \]

\[ \text{+ iso} \quad \text{+ anti- IL-22} \]

\[ \text{pStat3 Y705} \]

\[ \text{Cyclin D1} \]

\[ \text{+ iso} \quad \text{+ anti- IL-22} \]

\[ \text{+ anti- IL-17} \quad \text{+ anti- IL-6} \]

\[ \text{+ iso} \quad \text{+ anti- IL-22} \]

\[ \text{live, CD45+, lin-, Thy1hi} \]

\[ \text{live, CD45+, lin-, Thy1hi} \]

\[ \text{live, CD45+, lin-, Thy1hi} \]
IL-22 sustains colon cancer

Kirchberger et al., JEM 2013
ILC promote colitis and sustain colon cancer through IL-22 production

Genetic control of bacteria-driven colon cancer (1.5Mb region on Chr 3—also acts in other models)

Functions in haematopietic cells to control early innate response to *H. Hepaticus*

DN 17+22+ Thy1+ ILC accumulate in CRC and mediate a functional role in perpetuation of the disease

IL-22 is required for pStat3 in IEC

Neutralisation of IL-22 ameliorates established cancer-cell extrinsic control of neoplastic cells

IL-22+ T and non-T cells in human CRC—novel therapeutic target

(Flavell, Nature 2012; Karin Nature 2012)
**Inflammatory cytokines contribute to the initiation and perpetuation of bacteria-driven colon cancer**

- Is there an IL-22 signature assoc with spontaneous CRC?
- Mutations in CAC?
- Is dysbiosia of the microbiota a contributor to Hh-driven CAC?
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M. Oukka (Benaroya Inst)
Paul Crocker (Dundee)

CRUK

wellcome trust

BBSRC
biodiscovery for the future

Fondation Louis-jeantet

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