Lymphotoxin links microbiota and group 3 ILCs to protect against intestinal inflammation

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Disclosures

No relevant disclosures

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Ligand-receptor interactions in Lymphotoxin/TNF system

LTβ3 LTα3 LTβ2 LTα1

TNF3

Broad expression

Lymphocytes
ILC, T, B

T, DC, Macrophages

Epithelial cells
T-cell, DC, Macrophages, Epithelial cells

TNF blockers for IBD

LTβR-modulating drugs in IBD?
LT expression is increased in the colon during epithelial injury.
LT expression is increased in inflamed tissue versus uninflamed tissue of Crohn`s disease patients

p=0.01*  
p=0.05*

*Sign test n=10

In collaboration with Scott Snapper. Boston Children`s Hospital
Correlation of $LT^\pm$ and $LT^2$ with IL-22 expression in IBD patients

*Pearson correlation coefficient test n=23
Development of ILC lineages

Hypothesis: LT regulates ILC3s

Diefenbach et al, Immunity 2014
LTβR-dependent protection against intestinal inflammation

anti-bacterial proteins RegIIIβ,γ

pathogen *C. rodentium*

epithelial cell

IL-22R

LTβR

LT

MNP

LTβR

IL-23

IL-22

B

Nph

T

RORγt+

ILC3

Lymphoid follicle

Wang et al, Immunity, 2010
Tumanov et al, Cell Host Microbe, 2011
Kruglov et al, Science, 2013
Macho-Fernandez et al, Mucosal Immunol 2015
LT and IL-22 expression is increased in the colon during epithelial injury

How is LT expression regulated during mucosal damage?
Antibiotic treatment reduces LT and IL-22 expression

Antibiotics 1mL/daily

Antibiotics (ampicillin 1g/L, gentamicin 1g/L, metronidazole 1g/L, neomycin 1g/L, vancomycin 0.5g/L) – 1mL/day, gavage
MyD88 signaling is critical for protection during DSS-induced injury and for IL-22 production.

**Graphs:**
- **Body weight change %**
  - WT vs. MyD88^-/-
  - Significance: ***P < 0.001, **P < 0.01*

- **Survival, %**
  - WT vs. MyD88^-/-
  - Survival rate decreases over days.

- **IL-22/HPRT mRNA**
  - WT > MyD88^-/-
  - Significance: *P < 0.05

- **Lta mRNA/HPRT**
  - WT > MyD88^-/-
  - Significance: *P < 0.05

- **Ltb mRNA/HPRT**
  - WT > MyD88^-/-
  - Significance: **P < 0.01

**Footnote:**
DSS 5% for 5 days
MyD88 signaling controls IL-22 production by ILC3s

Lineage = B220, CD3, CD5, CD11b, CD11c, Gr1, Ter119

Thy1.2+Lin- gated

Wildtype

DSS 5% for 5 days

Thy1.2+Lin+ gated

MyD88-/-

0.0

0.3

2.2

0.1

IL-22

RORγt
Stimulation of LTβR signaling in MyD88−/− mice increases IL-22 production

Agonistic anti-αLTβ ab, 150 μg, day 3

**ns**
Hypothesis: LT signaling links signals from microbiota via MyD88 pathway to activate ILC3 for mucosal protection
Lymphotoxin signaling inhibits colitis-associated cancer development

AOM (12.5 mg/kg)

-/-

0 5 10 15 20 25 30

Number of tumors/colon

% of tumour size (diameter)

<3mm

3-5mm

>5mm

-/-

0 5 10 15 20 25 30

Number of tumors/colon

Ltb-/-

WT

Lymphotoxin signaling inhibits colitis-associated cancer development
Formation of reactive oxygen species is associated with IBD
Conclusions

- LTβR signaling in intestinal epithelial cells is essential for protection against epithelial damage

- LT regulates IL-22 production by group 3 ILCs for mucosal protection

- LT and IL-22 expression by ILC3 is regulated by MyD88 signaling

- LTβR agonists promote IL-22-mediated mucosal healing

- LTβR protects against colitis-associated cancer

- Electrochemically-based detection of reactive oxygen species in intestine using biosensors for diagnostics and understanding the mechanism of early inflammation
Collaborators

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Finding

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