Disclosure

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Adaptive Immune Responses in IBD

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Immunological Factors in IBD: Crohn’s Disease
NOD2/CARD15—receptor for peptidoglycans (MDP); induces NF-κB activation

- CARD: C-terminal caspase recruitment domain
- NBD: Nuclear binding domain
- LRR: Leucine-rich repeat (recognition of peptidoglycans)

3 mutations in LRR increase susceptibility to CD (failure to bind MDP)

IL-12p70 Production by Splenic CD11b+ cells in the Presence or Absence of MDP

NOD2 \(^{+/+}\) vs NOD2 \(^{-/-}\)

- LPS
- PGN
- Pam\(_3\)Cys
- Loxoribine
- dsRNA
- CpG

MDP 0 μg/ml
MDP 10 μg/ml
MDP 100 μg/ml

pg/ml
NOD2 Transgenic Mice have a decreased Expression of NFκβ Components
NOD 2 Transgenic Mice have an increased resistance to PGN-induced colitis

Yang and Fuss et al   Submitted
NOD2 is a negative regulator of TLR2-mediated TH1 responses

T. WATANABE, A. KITANI, P. MURRAY and W. STROBER. Nat Immunol 2004; 5: 800-808
Key Inflammatory Mediators in Crohn’s Disease

- Antigen
- APC cell
- T cell
- CD4

Activated
- Macrophage
- IL-12
- IFN-γ

Activated
- T cell
- Th1

IL-10
- TGF-β

Treg

TNF-α
- MAC
- NF-κβ
IL-1β
IL-6
Treatment of Colitis by Inhibition of Th$_1$

Colitis Treatment Attenuated/

Anti-TNF$_{\alpha}$ Anti-IFN$_{\gamma}$ Anti-IL-12 No Colitis

Th$_1$
Infliximab-Treated Patients with Crohn’s Disease

Clinical response defined as a ≥ 70-point decrease in CDAI score from baseline.

Clinical remission defined as a CDAI score < 150.

4-Week clinical response

- Placebo (n=25): 17%
- Infliximab 5, 10, and 20 mg/kg (n=83): 64%

4-Week clinical remission

- Placebo (n=25): 4%
- Infliximab 5, 10, and 20 mg/kg (n=83): 33%

p=0.001
p=0.005

Infliximab Induces Activated T-Cell and APC Apoptosis

Lugering et al, Gastro v. 121, 2001
Ten Hove et al, Gut v. 50, 2002
Response and Remission Rates after Anti-IL-12 Treatment: Regimen II

Mannon and Fuss et al. NEJM 2004
Lamina Propria Mononuclear Cell Cytokine Secretion Before and After Anti-IL-12 Treatment

**IL-12**

Pre: 153.1 ± 51.1 pg/ml  
Post: 2.8 ± 2.6 pg/ml  
P value: 0.028

**IFN-γ**

Pre: 9,835.4 ± 3,555.8 pg/ml  
Post: 1,078.8 ± 354.4 pg/ml  
P value: 0.053

**TNF-α**

Pre: 3,486.8 ± 576.1 pg/ml  
Post: 1,062.8 ± 281.9 pg/ml  
P value: < 0.01
Interleukin-12

- Recently discovered cytokine, p19/p40 heterodimer
- Evolving role in inflammatory disease (Sustaining of memory T cells, role in susceptibility to EAE and RA)

Interleukin-23

- Initially thought to induce the differentiation of IL-17, IL-6, TNF-α secreting T Cells
Lamina Propria Mononuclear Cell Cytokine Secretion Before and After Anti-IL-12 P40 mAb Treatment

**IL-23**

<table>
<thead>
<tr>
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<th>Pre</th>
<th>Post</th>
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<tr>
<td></td>
<td>175 ± 63.0</td>
<td>25.0 ± 12.0</td>
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<tr>
<td><strong>P value</strong></td>
<td>0.03</td>
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Graph showing the secretion levels of IL-23 (in pg/ml) before (Pre) and after (Post) treatment.
Lamina Propria Mononuclear Cell Cytokine Secretion Before and After Anti-IL-12 Treatment

**IL-17**

- **Pre**: 141 ± 60.0
- **Post**: 12.1 ± 3.0
- **P value**: 0.03

**IL-6**

- **Pre**: 1355 ± 501
- **Post**: 54 ± 19
- **P value**: 0.02
Regulation of IL-17-Producing Effector CD4+ T Cells

Old model
- IL-12
- IL-23
- IL-23R
- IFN-γ
- IL-4
- TH1
- TH2
- TH17

New model
- IL-12
- IL-23
- IL-17
- TH1
- TH2
- TH17

Harrington et al Nat Immun 2005
TA Wynn Nat Immun 2005
Regulation of IL-17-Producing Effector CD4+ T Cells

Harrington et al Nat Immun 2005

TA Wynn Nat Immun 2005
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Regulation of IL-17-Producing Effector CD4+ T Cells

Harrington et al Nat Immun 2005

TA Wynn Nat Immun 2005
Immunological Factors in IBD: Ulcerative Colitis
NKT Cells and IL-13 in Ulcerative Colitis

Heller et al Gastroenterology 2005
Fuss et al J Clin Invest 2004
IL-13 and IFN-γ Secretion by IBD LPMCs

Fuss et al J Clin Invest 2004
IL-13 Production By UC LPMC’s in Response to CD1d-Expressing Stimulator Cells
IL-13 Enhances Cytotoxicity of NKT Cells

A

- HT-29
- HT-29+NKT
- HT-29+NKT+IL-13

B

- HT-29
- HT-29+NKT
- HT-29+NKT/IL-13

Invariant NK T cell line

Ulcerative Colitis NK T Cells
IL-13 caused a dose-dependent decrease in electrical resistance of HT-29 epithelial cell monolayers.

- This was associated with an increase in the cellular apoptotic rate.

- Addition of IL-13 in vitro led to an increased expression of the pore-forming tight junction protein claudin-2.
IL-4 and IL-13 Receptor Signaling Pathways

[Diagram showing signaling pathways for IL-4 and IL-13 receptors, including receptor activation, signal transduction, and transcription]
Increased IL-13Rα2 Bearing NK T Cells in LPMC of Ulcerative Colitis Patients
IL-13 Secretion from Ulcerative Colitis Patient LPMC After Treatment with IL-13 Pseudomonas Exotoxin
Treatment of Oxazolone Colitis with a IL-13 Pseudomonas Exotoxin

% Weight Day 0 vs. Days

- Ethanol
- Oxazolone 6 mg
- Oxa 6mg + IL-13 PE
Treatment of Oxazolone Colitis with a IL-13 PE leads to Decreased IL-13 Secreting Cells
NKT Cells and IL-13 in Ulcerative Colitis

Heller et al Gastroenterology 2005

Fuss et al J Clin Invest 2004
TNF-α in the Presence of IL-13 Can Augment the Expression of IL-13 Receptors
Gut lumen

M cells

Bacteria, antigens

Lumenal factors

APC

Th0

IL-12

Th0

IL-23

Th1/IL-17

TNFα

IFN-γ

Th1

NK T cell

IL-13

TNFα

MΦ

IL-13
Regulation of IL-17-Producing Effector CD4+ T Cells
Regulation of IL-17-Producing Effector CD4+ T Cells
Regulation of IL-17-Producing Effector CD4+ T Cells