Innate immunity as a therapeutic target in IBD

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The intestinal mucosa must rapidly recognize luminal pathogens to initiate controlled immune responses, but maintain hypo responsiveness to harmless commensals.
Innate immune cells express so-called pattern recognition receptors (PRRs), that specifically discriminate between self and microbial non-self, based on the recognition of broadly conserved molecular patterns.
Families of PRRs: TLRs, NLRs, ...
TLR-KO mice are susceptible to acute DSS colitis

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Colitis - Model</th>
<th>Activity</th>
<th>Knockout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic damage (target: IEC)</td>
<td>DSS - acute</td>
<td>↑↑↑</td>
<td>TLR2-/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TLR4-/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TLR9-/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MyD88-/-</td>
</tr>
</tbody>
</table>

↑↑↑ Epithelial injury

Gastro 2007 132:1359
Cell 2004;118:229
Some TLR5KO develop spontaneous colitis which is TLR4-dependent.
Treatment with TLR2 agonist ameliorates all clinical signs of DSS-induced colonic inflammation.
The TLR2 ligand PCSK attenuates severity of DSS colitis
TLR2 stimulation induces ZO-1 redistribution via PKC which correlates with TER increase.

Gastroenterology 2004;127:224
PCSK-treatment leads to substantial preservation of TJ/AJ architecture of IEC in DSS colitis

PCSK-treatment leads to substantial preservation of TJ/AJ architecture of IEC in DSS colitis

ZO-1

E-cadherin

DSS 2.7%, Day 12

* inflammatory infiltrate

Gastro 2007 132:1359
DSS-mice treated with TLR2 agonist demonstrate lower FITC-dextran serum levels.
Epithelial cell TLR engagement stimulates extension and antigen sampling of underlying dendritic cells.

J Immunol 2006 176:4275
Immunity 2006 24:623
Science 2005 307:254
Nat Immunol 2001 2:361
TLR inhibition protects against TH1-mediated colitis

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<tbody>
<tr>
<td>Toxic damage (IEC, T cell etc.)</td>
<td>DSS – chronic</td>
<td>↓↓↓</td>
<td>TLR9-/-</td>
</tr>
<tr>
<td>T-cell-mediated</td>
<td>TNBS</td>
<td>↓↓↓</td>
<td>TLR4-/-</td>
</tr>
<tr>
<td></td>
<td>x Stat3mutant</td>
<td></td>
<td>TLR4-/-</td>
</tr>
<tr>
<td></td>
<td>x IL10/-</td>
<td></td>
<td>MyD88-/-</td>
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Cell Res 2006;16:70

Gastroenterology 2005;129:913
TLR4/MyD88 trigger chronic intestinal inflammation through aberrant myeloid cell activation in the absence of IL-10

MyD88/IL-10-/-

TLR4/Stat3-/-

IL-10-/- TLR-/-

= TH1

Histopathologic score

Control
TLR4 mutant
Stat3 mutant
TLR4/Stat3 mutant

Colitis score

0 5 10 15 20

* *
TLR4 blockage with CRX-526 ameliorates spontaneous colitis in MDR1α-deficient mice

MDR1α-deficient mice

- Severe colitis
- No colitis

• synthetic lipid A mimetic
• TLR4 antagonist

J Immunol 2005 174:6416
TLR signalling may not be involved in all forms of chronic murine colitis

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<td>T-cell-mediated</td>
<td>x IL2/-</td>
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<td>MyD88/-</td>
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<tr>
<td></td>
<td>CD4+CD62L+ T cell transfer</td>
<td></td>
<td>TLR9/-</td>
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</table>

MyD88/IL2-/-

IL-27

STOP

iTreg

Th17

Immunity 2006;25:1
Eur J Immunol 2007;37:1809
Two autophagy-genes ATG16L1 and IRGM have been associated with CD.

ATG16L1

Nat Genet. 2007 39:207
Nat Genet. 2007 39:596
Nat Genet. 2007; 39:830
MyD88-dependent signalling pathways contribute to intestinal tumor progression.
NOD2-overexpression protects against peptidoglycan- and TNBS-colitis

J Clin Invest 2008 118:545
Gastroenterology 2007 133:1510
Basal innate immune signaling may be protective of the IEC barrier against acute injury.
Aberrant innate immune signaling may favor chronic intestinal inflammation through commensal-mediated proinflammatory TH1-effects in the lamina propria.

Chronic inflammatory disease

Gut. 2005 Aug;54(8):1182-93