Advances in IBD Pathogenesis: Translating Biology into the Clinic

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IBD: a central problem in the relationship between the microbiota, epithelium and immune system

- Genetic susceptibility
- Microbial flora
- PRR signals, metabolites
- Interepithelial
- Environmental factors
- Diet, hygiene
- Stress
- NLRs, smoking

Crohn’s disease
Ulcerative colitis
Both CD & UC

Arthur Kaser, Sebastian Zeissig, and Richard S. Blumberg
GWAS success: approximately 160 IBD loci

Franke et al, Nat Genet 2010
Anderson et al, Nat Genet 2011

Why So Many IBD Genes: Evolution or Creation?
Shared genetic underpinning of many immune-mediated disorders

Evolution of IBD

• Do genes that predispose to IBD confer a survival advantage through protection against infections?
• An exuberant Th1/Th17 response or diminished regulatory activity may have been selected by endemic infectious organisms in populations.
  – Under modern environmental pressures, leads to other problems.

MSMD, Mendelian susceptibility to mycobacterial disease
Your Intestinal Bacteria

Are we only 10% Human?

Lots of bacteria
50% of fecal solids
>400 species
Most non-culturable
Provide 40% energy
Other life forms undefined
Archaea
Fungi
Protists
Viruses

10^{13} - 10^{14}

Your Intestinal Bacteria
from Jon Braun, UCLA

Normal Colon:
Controlled/physiologic inflammation

lumen

lamina propria

*GC, goblet cells
Applying molecular pathogenesis to the clinic

Development of new therapies in IBD:

A few successes, but mostly failures
Therapeutic targeting of innate immune pathways

Innate Immune Signaling: NF-κB Activation Cascade

TNF, IL-1β → NEMO (IKKγ) → IKKα → IKKβ → IκB → Ub → IκB Degradation → NF-κB → nucleus → TNF, IL-12/23
Immunotherapy of IBD is like the real estate market: It’s all about timing and location

8K-NBD Ameliorates Colitis in IL-10⁻/⁻ Mice

Epithelial NEMO Links Innate Immunity to Chronic Intestinal Inflammation

Timing and Location

- **Mucosal Homeostasis**
  - NF-κB (TLR) inhibition detrimental
- **Mucosal Inflammation**
  - NF-κB (TLR) inhibition beneficial
- **Intestinal Epithelium**
  - NF-κB (TLR) inhibition detrimental
- **Lamina Propria**
  - NF-κB (TLR) inhibition beneficial
Cytokine/cytokine receptor pathways

Genetic Associations in the IL-12/23 Pathways

Blockade of T-cell differentiation

Ustekinumab induction and maintenance therapy in refractory Crohn's disease

![Diagram showing the mechanism of ustekinumab in Crohn's disease](image)

- **Placebo** (N=132)
- **Ustekinumab** 1 mg/kg (N=131)
- **Ustekinumab** 3 mg/kg (N=132)
- **Ustekinumab** 6 mg/kg (N=131)

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Ustekinumab 1 mg/kg</th>
<th>Ustekinumab 3 mg/kg</th>
<th>Ustekinumab 6 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>16.7%</td>
<td>27.9%</td>
<td>30.5%</td>
<td>32.1%</td>
</tr>
<tr>
<td>6</td>
<td>23.5%</td>
<td>36.6%</td>
<td>34.1%</td>
<td>31.8%</td>
</tr>
<tr>
<td>8</td>
<td>17.4%</td>
<td>39.7%</td>
<td>41.5%</td>
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Crohn’s disease: Primary endpoint at week 6 shows no treatment benefit of secukinumab

IL-12/23 in IBD

- Role of IL-12/23 established
  - Is it IL-12, IL-23 or both?
- Downstream effectors less clear
  - Probably not IL-17A or F
  - Probably not IFN-γ
  - Other IL-17 FMs
  - IL-21
  - IL-22: homeostatic role
  - Innate effects of IL-23
Costimulatory Pathways

CTLA4-Ig Binds to B7 and Inhibits CD28-B7 Interactions
Hypothesis: IBD is RA of the Gut

Abatacept results in CD and UC

Abatacept CD
Clinical Remission (CDAI ≤ 150) day 57 and 85

Abatacept UC
Clinical Remission (Mayo Score ≤2) day 85

Ulcerative colitis during CTLA-4lg therapy in a patient with rheumatoid arthritis
L M Amezcuá-Guerra, B Hernández-Martinez, C Pineda and R Bojalil
Gut 2006:55;1059-1060
doi:10.1136/gut.2006.095539

Location: Tregs play a special role in the gut

Oral Janus Kinase (JK) Inhibitor Rationale

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Effects on the immune system</th>
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<tr>
<td>IL-2</td>
<td>Stimulate the proliferation and differentiation of Th, Tc, B, and natural killer (NK) cells</td>
</tr>
</tbody>
</table>
| IL-4     | Induce the differentiation of TH0 to TH2
Induce immunoglobulin switching |
| IL-7     | Promote the development, proliferation and survival of T, B, and NK cells |
| IL-9     | Stimulate intrathymic T cell development |
| IL-15    | Promote the proliferation, cytotoxicity and cytokine production of NK cells |
| IL-21    | Enhance T and B cell function |

- Tofacitinib (CP-690,550) is a novel, small-molecule, oral JAK inhibitor
- Tofacitinib inhibits JAK1, JAK2, and JAK3 in vitro with functional cellular specificity for JAK1 and JAK3 over JAK2. Importantly, tofacitinib directly or indirectly modulates signaling for an important subset of pro-inflammatory cytokines including IL-2, -4, -7, -9, -15, and -21

Sandborn W et al. DDW 2011
Tofacitinib, an Oral Janus Kinase Inhibitor, in Active Ulcerative Colitis

Adhesion and Homing
Mucosal and inflammatory zip codes

α4 Integrin
β1
β7
Chemokines
CCR9 ligands
VCAM-1
MAdCAM-1

Progressive Multifocal Leukoencephalopathy

Alters T and B cell functions

Prevents entry of T and B cells into organs by blocking binding to "adhesion" integrins

Natalizumab
(IMS, Crohn's disease)

Rituximab
(hematologic malignancies)

Ethalizumab
(psoriasis)

Alters T and B cell functions

Brain
Bone marrow
Kidney, Skin

Gut

leukocyte

natalizumab

natalizumab

Vedolizumab
rhuMab-beta7

PF-00547659

endothelium

integrins

addressins

VCAM-1

MadCAM-1

Major EO. 2010.
Annu. Rev. Med. 61:35–47
GEMINI I – Vedolizumab for the Maintenance of UC

Primary and Secondary Outcomes Through 52 Weeks


Challenges…some final thoughts

• Getting the therapy to the right patient and at the right time will require markers for stratification

• Plasticity of the immune system and the emergence of alternative inflammatory pathways are important considerations

• Understanding the unique properties of the gut relative to other tissues
  – Also provides unique opportunities for local delivery

• Inevitable concerns of immunosuppression