An Integrated Classification of IBD: The Current Paradigm of Crohn’s versus UC

- An integrated classification implies:
  - more diagnostic certainty based on
  - interdependent characteristic mechanisms of disease that point to
  - application of more effective disease-specific treatments

- Accepted criteria by endoscopic, imaging, histologic findings
- No pathognomonic markers
- Histology and Anatomy: no new signatures (except UC-like Crohn’s disease)
- Serology for anti-microbial antibodies

Bacterial flagellin is a dominant antigen in Crohn disease

- Ch3/HeJBir substrain bred for the phenotype of spontaneous colitis and perianal inflammation; B and T cell reactivity to enteric microbial antigens
- Th1 CD4 cell reactivity to flagellin, which transfers colitis to SCID mice
- Crohn’s disease (not UC, HC) had serum IgG to these flagellins
- Unique among protein antigens in that it is recognized by T cells and by pattern recognition receptors as a TLR5 ligand; this drives anti-flagellin responses and establishes flagellin as an adjuvant
- A TLR5 dominant negative polymorphism (flagellin unable to activate NF-kB) blocks development of anti-flagellin Abs (and is associated with decreased Crohn’s risk in susceptible populations)
B Cells Engage T Cells in an Antigen-Specific Manner

T cell-dependent B cell Ig class switching: the antigen link

Goyette et al., Nature Genetics 2015

Table 3: Comparing risk model for disease complications and early anti-HPA comparative efficacy analyses

<table>
<thead>
<tr>
<th>Complicating factor</th>
<th>Ref (95% CI)</th>
<th>p-value</th>
<th>Ref (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD (ICD-10 556.0)</td>
<td>1.0 (1.0-1.0)</td>
<td>0.05</td>
<td>1.0 (1.0-1.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Interstitial Keratitis</td>
<td>0.5 (0.4-0.6)</td>
<td>0.05</td>
<td>0.5 (0.4-0.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.6 (0.5-0.7)</td>
<td>0.05</td>
<td>0.6 (0.5-0.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Osteoporosis + CD</td>
<td>0.4 (0.3-0.5)</td>
<td>0.05</td>
<td>0.4 (0.3-0.5)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Odds Ratios for HLA Alleles Providing Risk for Crohn’s versus UC

An Integrated Classification of IBD: Genetic Signatures

- GWAS studies have now identified >200 risk loci
- Few coding region mutations (SNPs)
- Over representation of risk SNPs in the healthy population
- Overlap of many risk loci between CD and UC
- Complex contribution by multiple genetic risk loci (with as yet unexplained functional consequences) interacting with environmental factors

An Integrated Classification of IBD: Serologic Determinants as a Clinical Biomarker

- So with the aberrant antibody response to certain flagellin molecules seen predominantly in CD
- And with shared but also restricted MHC II molecules between CD and UC
- It may be that TCR repertoire, patterns of antigen recognition may be another way to define the spectrum of IBD
An Integrated Classification of IBD: 
Monogenic Disease-associated IBD


Immune Defects and IBD: 
Very Early Onset Colitis in Babies with IL-10 Pathway Deficiency


An Integrated Classification of IBD:
• Is there a third form of IBD, isolated colonic Crohn's
• The terminal ileum may be a separate organ, affected differentially by genetic risk and environment

An Integrated Classification of IBD:
Ileal vs Colonic Crohn's

An Integrated Classification of IBD:
A third type of IBD


An Integrated Classification of IBD:
A third type of IBD

Table 10: A summary of the distinguishing features of the three IBD: Inflammatory bowel disease, CD, isolated colonic CD, UC

<table>
<thead>
<tr>
<th>Feature</th>
<th>Crohn's Disease</th>
<th>Inflammatory bowel disease</th>
<th>Isolated colonic CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Highly common in joint (JIA)</td>
<td>Genotype linkage between CD and UC</td>
<td>Isolated colonic CD (not UC)</td>
<td></td>
</tr>
<tr>
<td>Lesion distribution</td>
<td>Croton-activated leukocytes (CRA)</td>
<td>UC-associated leukocytes (ULC)</td>
<td>Croton-activated leukocytes (CRA)</td>
<td></td>
</tr>
<tr>
<td>Histopathology</td>
<td>Neutrophils + T-cells</td>
<td>Neutrophils + T-cells</td>
<td>Neutrophils + T-cells</td>
<td>Neutrophils + T-cells</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>Partial response</td>
<td>Partial response</td>
<td>Partial response</td>
<td>Partial response</td>
</tr>
<tr>
<td>Endoscopic activity</td>
<td>Reduced activity</td>
<td>Reduced activity</td>
<td>Reduced activity</td>
<td>Reduced activity</td>
</tr>
<tr>
<td>Microbiome analysis</td>
<td>No changes observed in 3 groups</td>
<td>No changes observed in 3 groups</td>
<td>No changes observed in 3 groups</td>
<td>No changes observed in 3 groups</td>
</tr>
</tbody>
</table>

An Integrated Classification of IBD: Epigenetic Signatures

- Epigenetics measures types of DNA and histone modifications
  - Methodology:
    - Bisulphite sequencing
    - Methylation sensitive high-resolution melting
    - Chromatin immunoprecipitation (ChIP) on Chip assays
  - Inherited and Acquired (Transient vs. Permanent)
  - Drugs that can Affect the Epigenome

- Interest in UC (and long-standing IBD inflammation) for hyper-methylation of DNA (especially genes involved in carcinogenesis)
- Discovery of hypermethylated gene “profiles” that may be disease-specific (potential biomarkers) Kang et al., Int. J. Mol. Sci. 2016, 17, 1291

PBMCs from CD and UC pts
- No bisulphite sequencing
- No differences in epigenetics signatures (97% of the differentially methylated positions were also seen in CD, but only 55% of the CD sites matched the UC)
- Disease activity and concomitant biologic med use did not affect results

Cytokine

Fahr et al. 2015 Nature
An Integrated Classification of IBD

- Current genetic risk loci reflect our appreciation for the spectrum that IBD spans
- Fine mapping of MHC alleles implicates more prominent role for the adaptive immune response in UC
- Intriguing data about restriction of gut mucosal epigenetic signatures and UC
- Intriguing data about restriction of B cell epigenetic signatures and CD
- Future studies need to aim to integrate genetic, epigenetic and functional measures to form a more complete picture of the mechanism of disease that can reveal novel points for intervention