Mechanisms of Disease:
The Science of IBD
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IBD Background and Disease Management
Inflammatory Bowel Disease
Description

- Group of idiopathic conditions characterized by chronic GI tract inflammation

- Most common subtypes are Crohn’s disease and ulcerative colitis

- Affects approximately 1.4 million Americans, 2.2 million Europeans, and 200,000 Canadians

IBD Symptoms and Complications

**Crohn’s Disease (CD)**
- Can affect any portion of the gastrointestinal tract, predominantly the ileum
- Potential transmural involvement of all tissue layers (full-thickness inflammation)
- Symptoms may include diarrhea, abdominal pain, weight loss, fever, perianal disease, signs of malnutrition, abdominal mass, and growth failure in children and adolescents
- Complications may include bowel obstruction, stricture, perforation, fistula, abscess, and cancer
- Increased risk of colorectal cancer
  - Related to length of disease (more than 8 to 10 years)
  - Related to length of colon involved

**Ulcerative Colitis (UC)**
- Limited to the colon and rectum
- Inflammation is limited to mucosal layer of colonic tissue
- Symptoms may include bloody diarrhea, abdominal pain, weight loss, fever, anemia, rectal bleeding, and signs of malnutrition
- Complications may include perforated bowel and toxic megacolon
- Increased risk of colorectal cancer
  - Related to length of disease (more than 8 to 10 years)
  - Related to length of colon involved

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In the US, the public health burden of IBD, including economic costs, is quite substantial.\(^1\)

Annual indirect costs are estimated at an additional $5.5 billion in the US, between €8 billion and €28 billion in Europe, and over $1 billion in Canada.\(^2-5\)

In addition, productivity losses due to absenteeism and short-term disability also contribute to the economic burden of IBD.\(^6\)

### Economic Burden of IBD

#### IBD Direct Costs ($5.2 Billion\(^a\) in US)\(^1\)

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<th>Outpatient Costs(^1)</th>
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\(^a\)$3.1 billion for CD, $2.1 billion for UC.\(^1\)

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Clinical and Social Challenges of IBD

Interference With Daily Activities

- In a survey of patients with IBD (n=5576 evaluable respondents) by European national IBD patient organizations affiliated with the EFCCA:
  - Approximately 75% of patients reported that symptoms affect ability to enjoy leisure activities.
  - Approximately 69% of patients reported that symptoms affect ability to perform at work.

Psychosocial Burden

- Results from two surveys (N=4514 evaluable respondents) of Canadian patients with IBD, or a similar bowel disorder, demonstrated higher rates of depression in adult patients compared to the general population.
- Delayed puberty and body image issues in some younger patients.
- Social awkwardness due to disease symptoms and medication side effects among some children and adolescents.

Clinical Features

- About 50% of patients with UC have a relapse in any year.
- Approximately 70% to 80% of patients with CD will require surgery within their lifetime.
- In one study of 30 patients with CD, recurrent inflammation was observed in 73% and 93% of patients 3 months and 1 year post-surgery, respectively.

EFCCA, European Federation of Crohn’s and Ulcerative Colitis Associations

Etiology and Pathophysiology
While the Causes of IBD Are Unknown, Several Hypotheses Have Been Suggested by Studies

- Over 100 potential susceptibility genes identified
- Genes involved in ability to recognize bacteria (e.g., NOD2) and autophagy (e.g., ATG16L1)
- Foreign substances (antigens) may be the direct cause of inflammation
- Bacteria may stimulate immune system to produce inflammation
- Once the inflammation is triggered, the IBD patient’s immune system has difficulty “turning off” the immune response

Risk Factors
- Age - more likely among younger patients
- Ethnicity - more likely among Caucasians, in particular Ashkenazi Jews
- Family history - 10 to 30 times greater risk if close relative has disease
- Geography - more common in US and Europe
- Smoking - Active smokers are more than 2 times as likely to develop CD than nonsmokers, but less likely to develop UC

The GI Tract Is a Tightly Controlled Environment

Intestinal Mucosa [microscopic view]
- Gut Lumen
- Mucus
- Epithelium
- Lamina Propria
- Lymphocyte
- Blood Vessel
- Endothelium

Intestinal Mucosa [microscopic view]
Normal Host Defenses in the Gut

- Tight Junctions Between Cells
- Protective Mucus Layer
- Dendritic Cell (Antigen Presenting Cell)
- Circulating Lymphocytes
- Bacteria and Dietary Antigens Within Gut Lumen
- Lymphocyte
- Lamina Propria
- Macrophage
Inflammatory Bowel Disease Reflects an Imbalance of Inflammatory Response

Disrupted Protective Mucus Layer

Dendritic cells

1. Sample luminal bacteria

2. Present antigen

3. Proinflammatory cytokines released (e.g., TNF-α, interleukins)

4. Increase in adhesion molecules

Increase in vascular permeability

TNFα is a key player in the inflammatory process

TNFα is a pleiotropic, proinflammatory cytokine that regulates essential biologic functions, such as\(^1\):

- Cell survival, proliferation, differentiation, and apoptosis
- Mediating the local inflammatory immune response
- Inducing the expression of other proinflammatory cytokines and chemokines

Accumulation of Excess Infiltrating Lymphocytes Is a Hallmark of IBD

Lymphocyte Migration Reflects the Presence of Tissue-Specific Adhesion Molecules

2. Butcher EC. Leukocyte-endothelial cell recognition: three (or more) steps to specificity and diversity. *Cell.* 1991;67(6):1033-1036.
Lymphocyte Trafficking and Inflammation
Lymphocytes Are Migratory Cells That Traffic to Specific Tissues

- Intricate system to guide lymphocytes to areas of inflammation\(^3\)
- Imprinting of activated lymphocytes allows for preferential migration into tissues\(^3\)

Lymphocyte Trafficking Requires a Multistep Adhesion Cascade


*Chemokines, C5a, PAF, LTB4, formyl peptides*
Lymphocyte Trafficking to the Gut

Several molecules are involved in the lymphocyte trafficking/adhesion cascade\(^1\):

- CCR9 chemokine receptor and its ligand CCL25
- \(\alpha4\beta7\) integrin and its ligand MAdCAM-1

However, only a few are responsible for mucosal specificity of the lymphocyte homing process. Among these are\(^2,3\):

- \(\alpha4\beta7\) integrin
- CCR9 chemokine receptor

Multiple Chemokines Have Been Implicated in IBD

- Chemokines are a family of small proteins that play an important role in recruitment and activation of lymphocytes\(^1,2\)

- Biological effects of chemokines result from binding to chemokine receptors\(^1,2\)

- Several chemokines and their receptors play a role in homeostasis of mucosal immunity and pathogenesis of IBD. Some examples include:\(^2\)
  - CCL20-CCR6
  - CCL25-CCR9
  - CCL28-CCR10

Lymphocyte Recruitment Into Gut Mucosa—Role of α4β7 and MAdCAM-1

- α4β7-MAdCAM-1 interactions likely mediate selective lymphocyte trafficking to normal GI mucosa and gut-associated tissues

α4β7 and MAdCAM-1 Implicated in IBD

- MAdCAM-1 expression is increased at sites of inflammation in IBD

- α4β7 and MAdCAM-1 adhesion mechanism may be closely involved in lymphocyte trafficking to the site of inflammation in the gut

In summary

- IBD is characterized by chronic GI tract inflammation, and can cause debilitating symptoms and serious clinical complications.

- The etiology of IBD likely involves a complex interplay of genes, environmental triggers, and immune-mediated reactions that culminate in chronic inflammation. Once the inflammatory process is triggered, the immune system has difficulty shutting down its response.

- TNFα is increased in the mucosa and serum of patients with IBD. The actions of TNFα contribute to the uncontrolled inflammatory response and ensuing intestinal tissue damage that are characteristic of IBD and some other inflammatory diseases.

- Although a number of molecules are involved in lymphocyte trafficking, only a few are responsible for mucosal specificity of the lymphocyte homing process.
  - Among these are the chemokine-receptor pair CCL25-CCR9 and the α4β7 integrin/MAdCAM-1 adhesion mechanism.