Overlap between Primary Sclerosing Cholangitis (PSC) and inflammatory bowel disease (IBD)

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Intestine-liver interactions

Portal circulation

Bile duct system

Right colon

Left colon
PSC and IBD: related inflammatory disorders

- PSC: 60-80% have IBD (UC more than CD)
- IBD
  - Ulcerative colitis: PSC present in 2.4-7.5%
  - Crohn’s disease: PSC present in 3.4%
- Inflammation: generalized response to infection and or injury
  - Time course: infection/injury → inflammatory response → healing/repair
  - PSC and IBD: the initial trigger is poorly defined
  - Organ-specific but also generalized (systemic)
Ulcerative colitis (UC) & Crohn’s disease (CD): phenotypic features

- Peak age of onset: 15-30 years of age—immune system age effects
- Symptoms: diarrhea, abdominal pain, intestinal bleeding, growth retardation
- Intermittent—inflammation/damage alternating with tissue repair
- CD: healing is variable: healing by fibrosis
Stricturing in IBD and PSC

**Stricture: B2 behavior**

**Fistulae: B3 behavior**

**Cholangiogram: PSC**
PSC & IBD

- Timing: diagnoses can be at anytime—the disease courses are not related to each other
- Location
  - More often extensive disease
  - Rectal sparing (?)
  - Often with backwash ileitis
- Increased risk of colorectal neoplasia (pre-cancerous or cancerous changes)
  - 4.79 x compared to UC without PSC. Right-side > left-side
  - Need colonoscopic surveying
- Intestinal inflammation: more often relatively quiescent
- Genetic approaches to define the earliest disease stages—identify new therapies
Human genetic approaches: 2006-2010

• Genome wide association studies (GWAS)
  – Type several hundred thousand markers
  – Need large numbers of cases: 1000-4000
  – Identified > 70 genetic regions associated in IBD
  – PSC-small studies: less common disease than IBD
    • Germany
    • Norwegian-US (Mayo clinic)
  – But: many genetic regions common between chronic inflammatory diseases—same genes between PSC & IBD?
PSC genetics: the MHC (major histocompatibility complex) is the major genetic factor for PSC & UC

- MHC complex (chromosome 6p): most genetically diverse region in the genome
- Recognition of “self” and “non-self”
- MHC Class I and II genes
  - Class I: present on all cells
  - Class II: present on special cells
Within the MHC: different association patterns between PSC & UC

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HLA MHC Complex

Human chromosome 6
Classes of genes involved in IBD: implications for therapy

Complex cell populations balancing pro- and anti-inflammatory pathways:
- cell-cell interactions mediated by cytokines—"interleukins"—between leukocytes

Epithelial barrier layer
Luminal Microbes (non-self)
Goblet cells
Microbial recognition
Epithelial defect?
Systemic circulation

Naïve CD4+
Mesenteric lymph node
Lymphocyte activation

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3
Theories on the overlap between PSC & IBD

• Same genes?
  – Not thus far—but present PSC genetics studies have been too small to tell for sure

• Shared functional defects?
  – Same epithelial defects?
  – Tendency toward healing by scarring/fibrosis?

• Interacting systemic/circulating factors
  – IBD→PSC: Increased circulation of intestinal microbial components (portal circulation)
  – PSC→IBD: Toxic biliary factors secreted→increased colon cancer risk (right-side)
New Genetic & Genomic approaches: Sequencing

- DNA
- RNA (tissue-specific—sequencing intestine, liver, peripheral blood white cells)
  - RNA → protein
  - Small RNAs: very stable, regulate expression of other genes
Screening mechanisms for new therapies

• High throughput screens to quickly test thousands of new therapies
• Key: identify the functional readout of interest
• Animal models
• Early studies in humans
Value of human-based research

• Intensive study of individual patients
  – complex disease with highly variable course

• Digital revolution & data deluge: unprecedented capacity to generate enormous datasets
  – Computational requirements significant

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