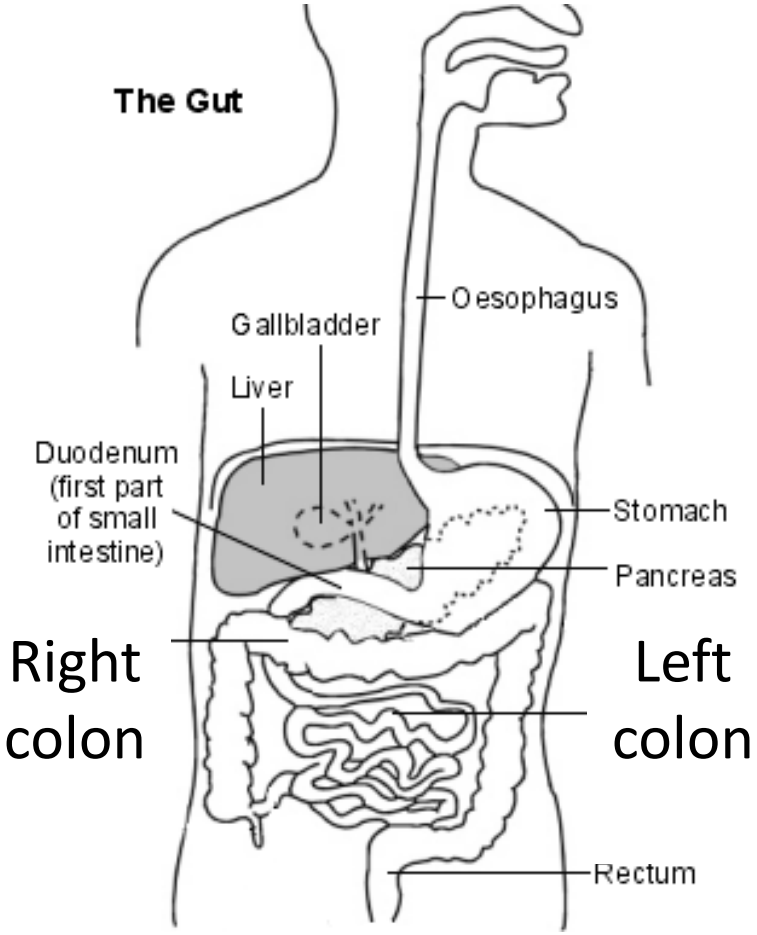
Overlap between Primary Sclerosing Cholangitis (PSC) and inflammatory bowel disease (IBD)

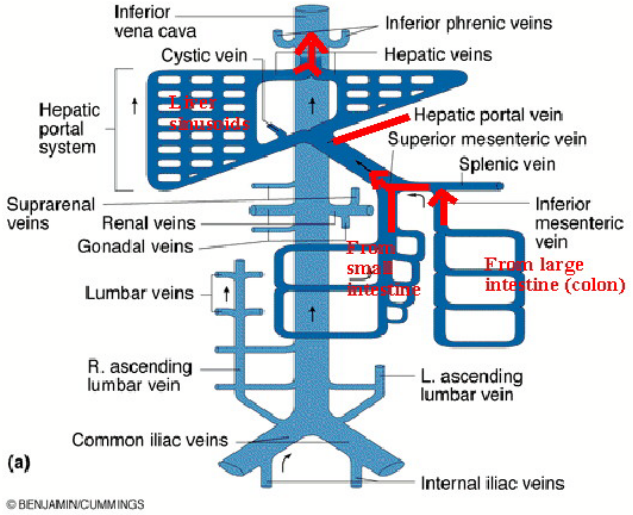
Judy H. Cho, M.D.

Yale University

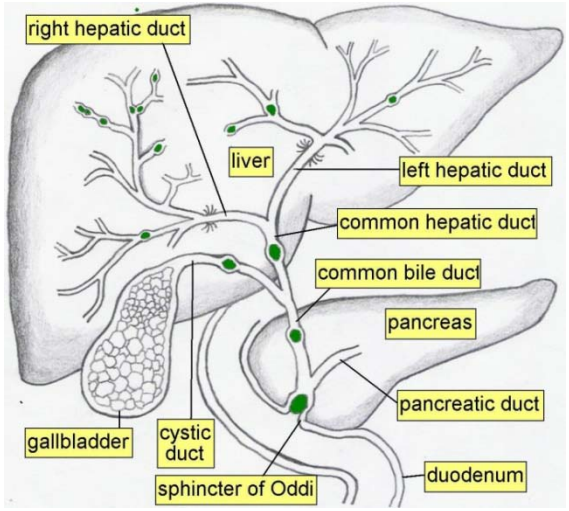
Intestine-liver interactions



Portal circulation



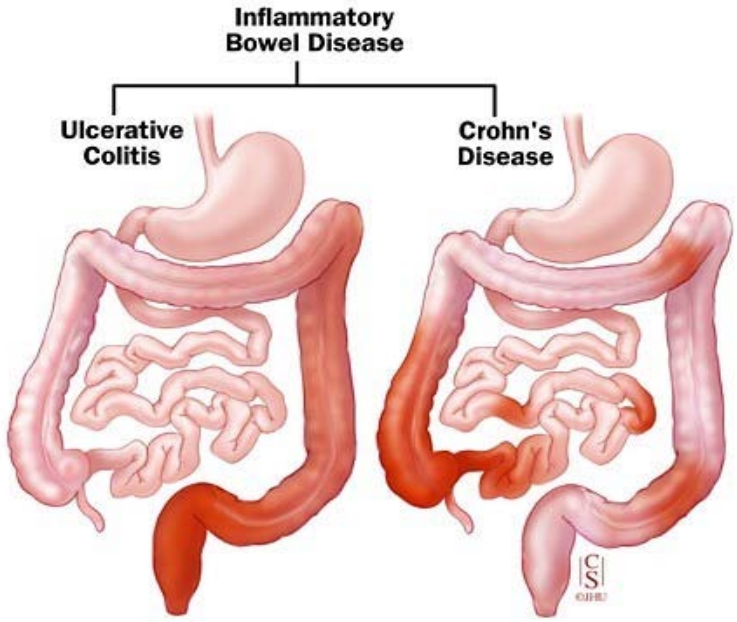
Bile duct system



PSC and IBD: related inflammatory disorders

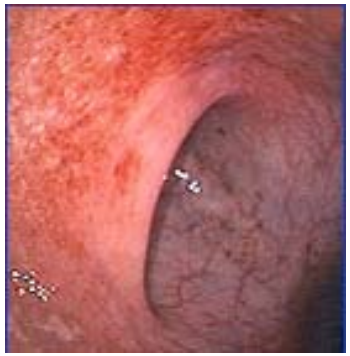
- PSC: 60-80% have IBD (UC more than CD)
- IBD
  - Ulcerative colitis: PSC present in 2.4-7.5%
  - Crohn's disease: PSC present in 3.4%
- Inflammation: generalized response to infection and or injury
  - Time course: infection/injury→inflammatory response→ healing/repair
  - PSC and IBD: the initial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

Ulcerative colitis (UC) & Crohn's disease (CD): phenotypic features

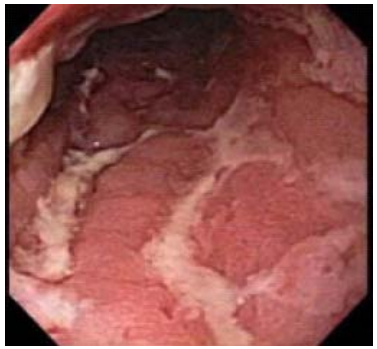


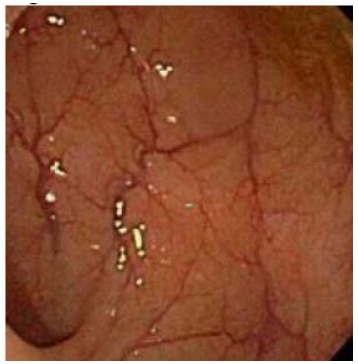
- Peak age of onset: 15-30 years of age—immune system age effects
- Symptoms: diarrhea, abdominal pain, intestinal bleeding, growth retardation
- Intermittent—inflammation/damage alternating with tissue repair
- CD: healing is variable: healing by fibrosis

UC



CD

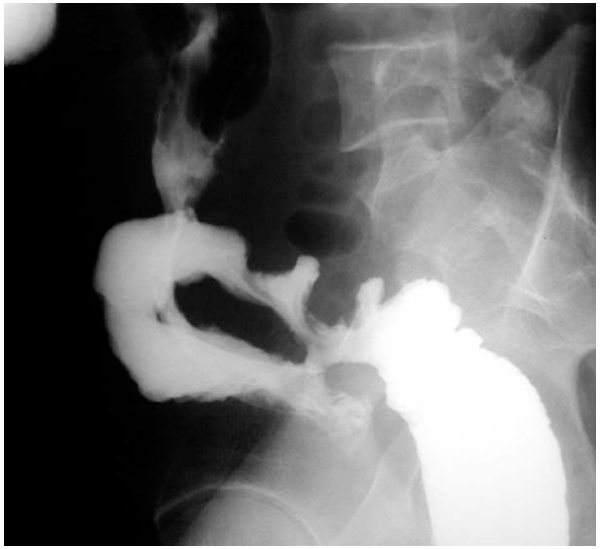




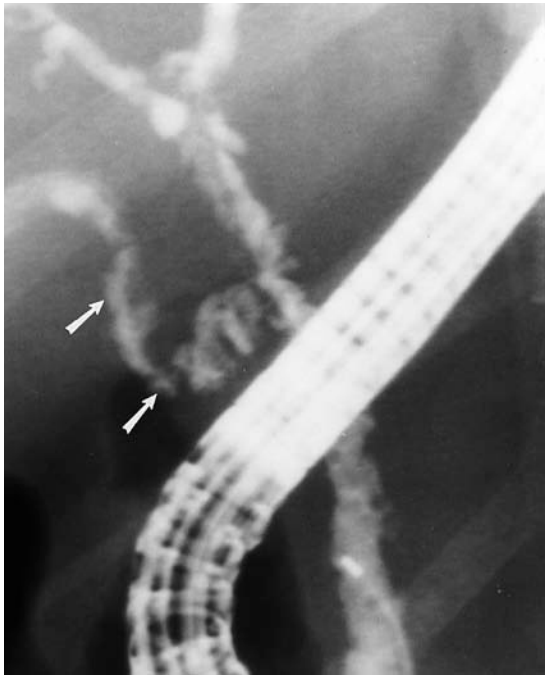
Stricturing in IBD and PSC

Stricture: B2 behavior

Fistulae: B3 behavior



Cholangiogram: PSC



PSC & IBD

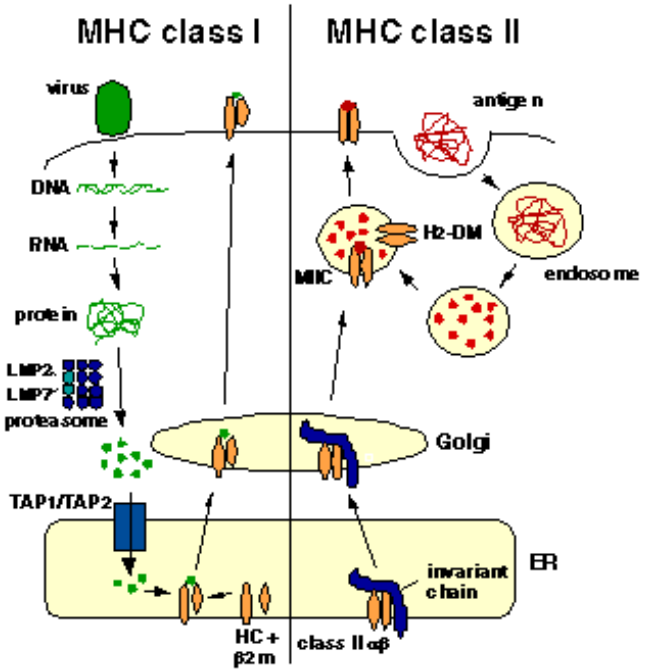
- Timing: diagnoses can be at anytime—the disease courses are not related to each other
- Location
  - More often extensive disease
  - Rectal sparing (?)
  - Often with backwash ileitis
- Increased risk of colorectal neoplasia (pre-cancerous or cancerous changes)
  - 4.79 x compared to UC without PSC. 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?

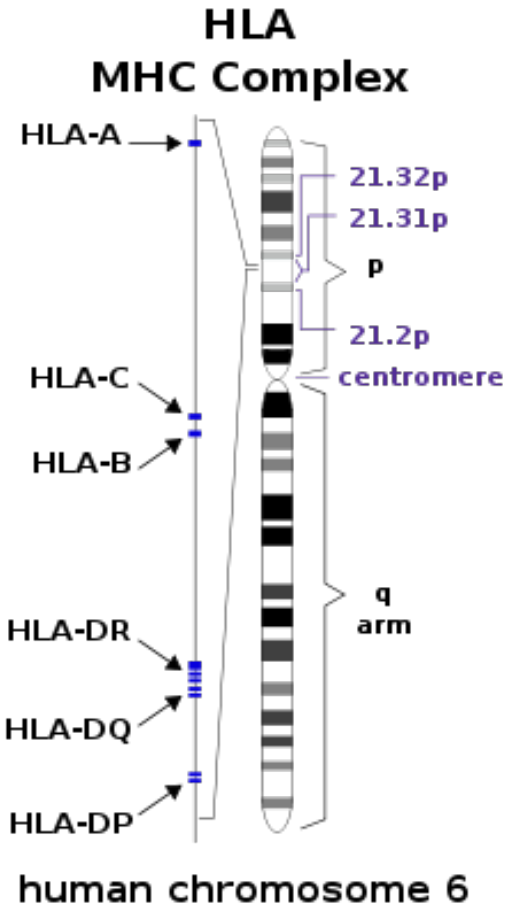
PSC genetics: the MHC (major histocompatibility complex) is the major genetic factor for PSC & UC

- 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

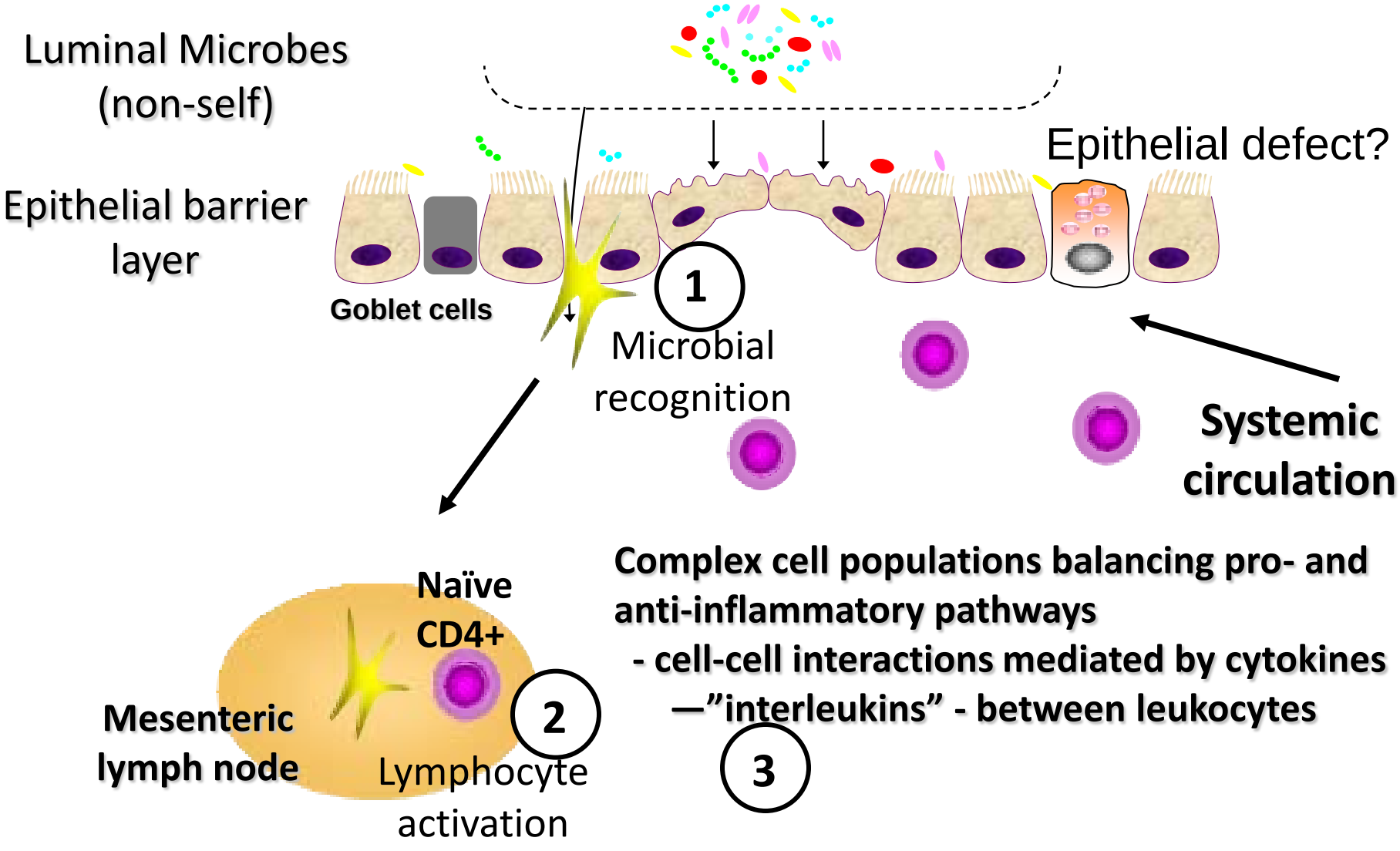


Within the MHC: different association patterns between PSC & UC

PSC	UC	
		Class I
++++	+	
+	+++	Class II



Classes of genes involved in IBD: implications for therapy



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
  - Computional requirements significant
- ibd@yale.edu