

# Biology and Pathobiology of Cholangiocytes: the key to understanding PSC

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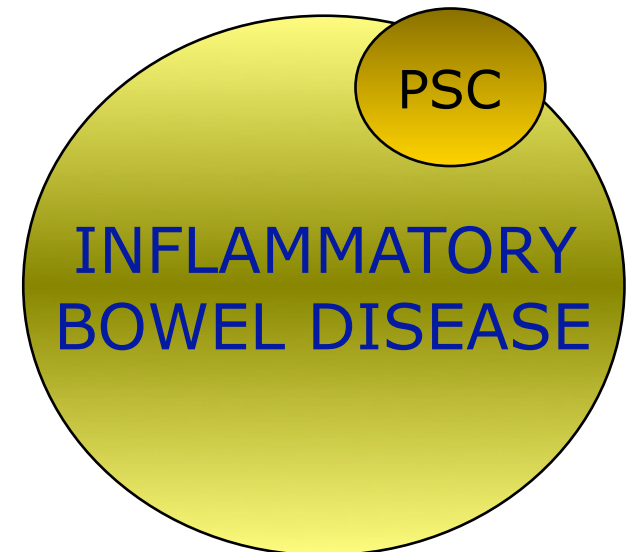
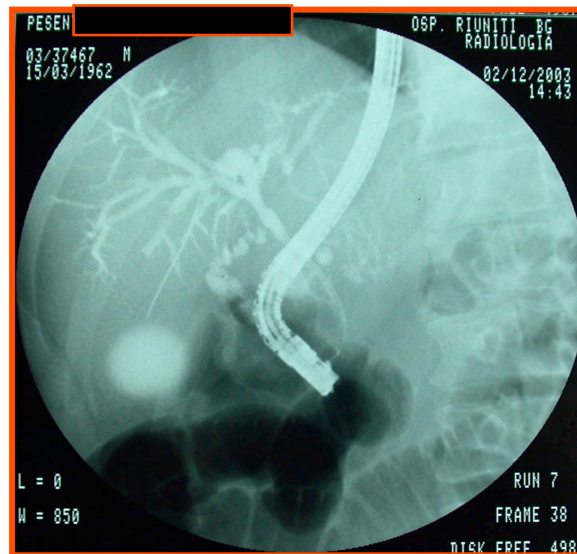
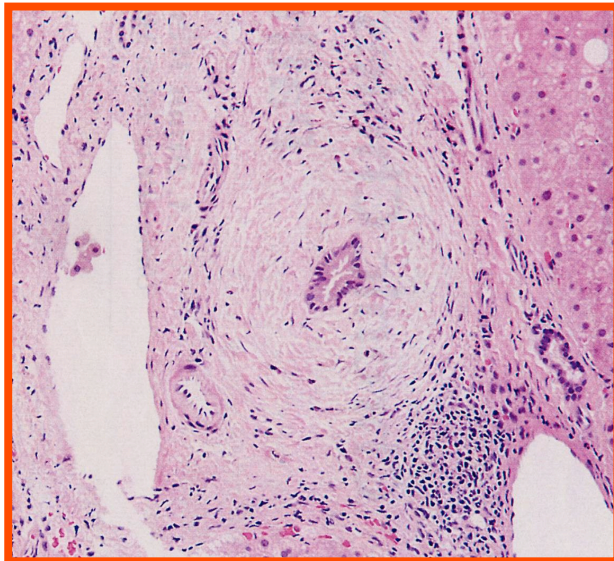
Scientific Director CeLiveR Network

University of Milan-Bicocca

# Defining features of PSC

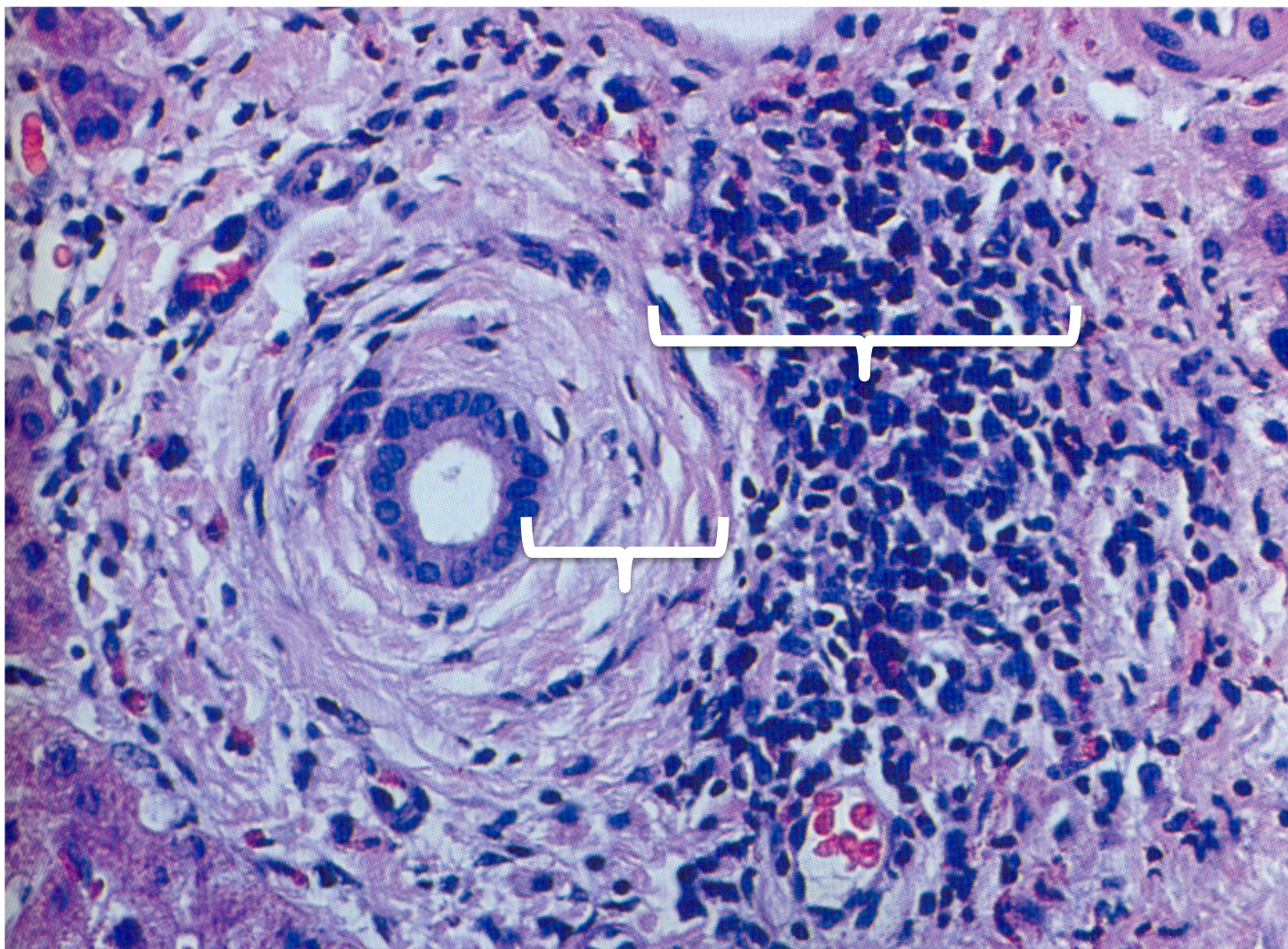
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- Bile duct damage with portal inflammation and peribiliary sclerosis
- Segmental bile ducts sclerosis and beading
- Association with IBD



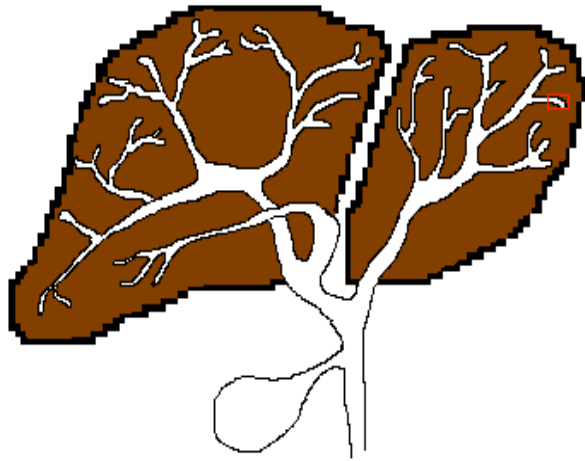
# PSC – histology

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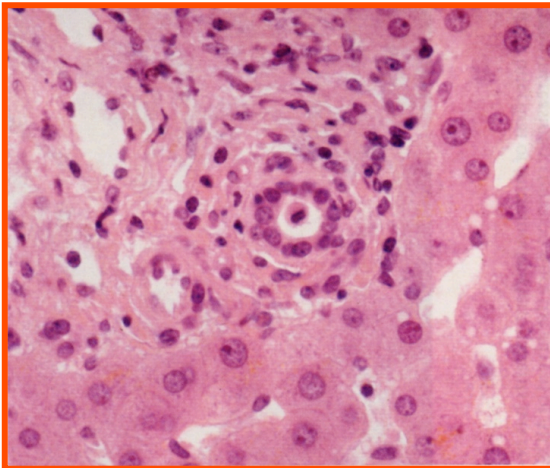


# Progressive biliary damage in PSC

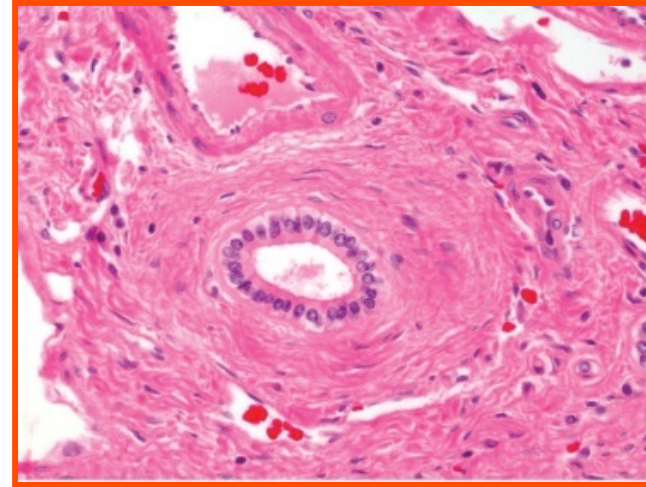
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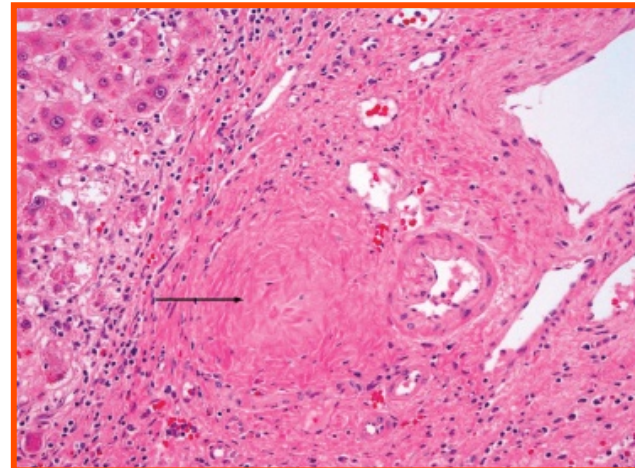
PSC stage II



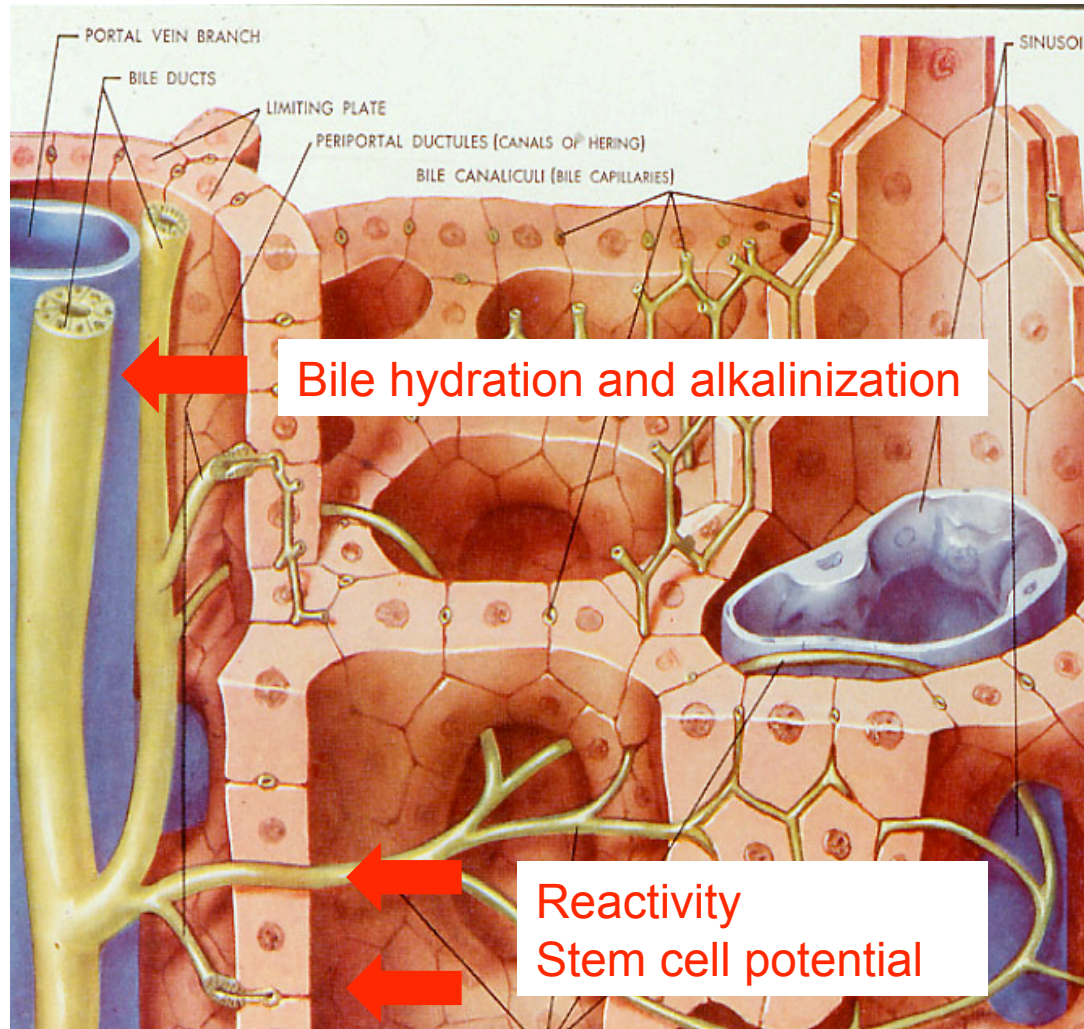
PSC stage III



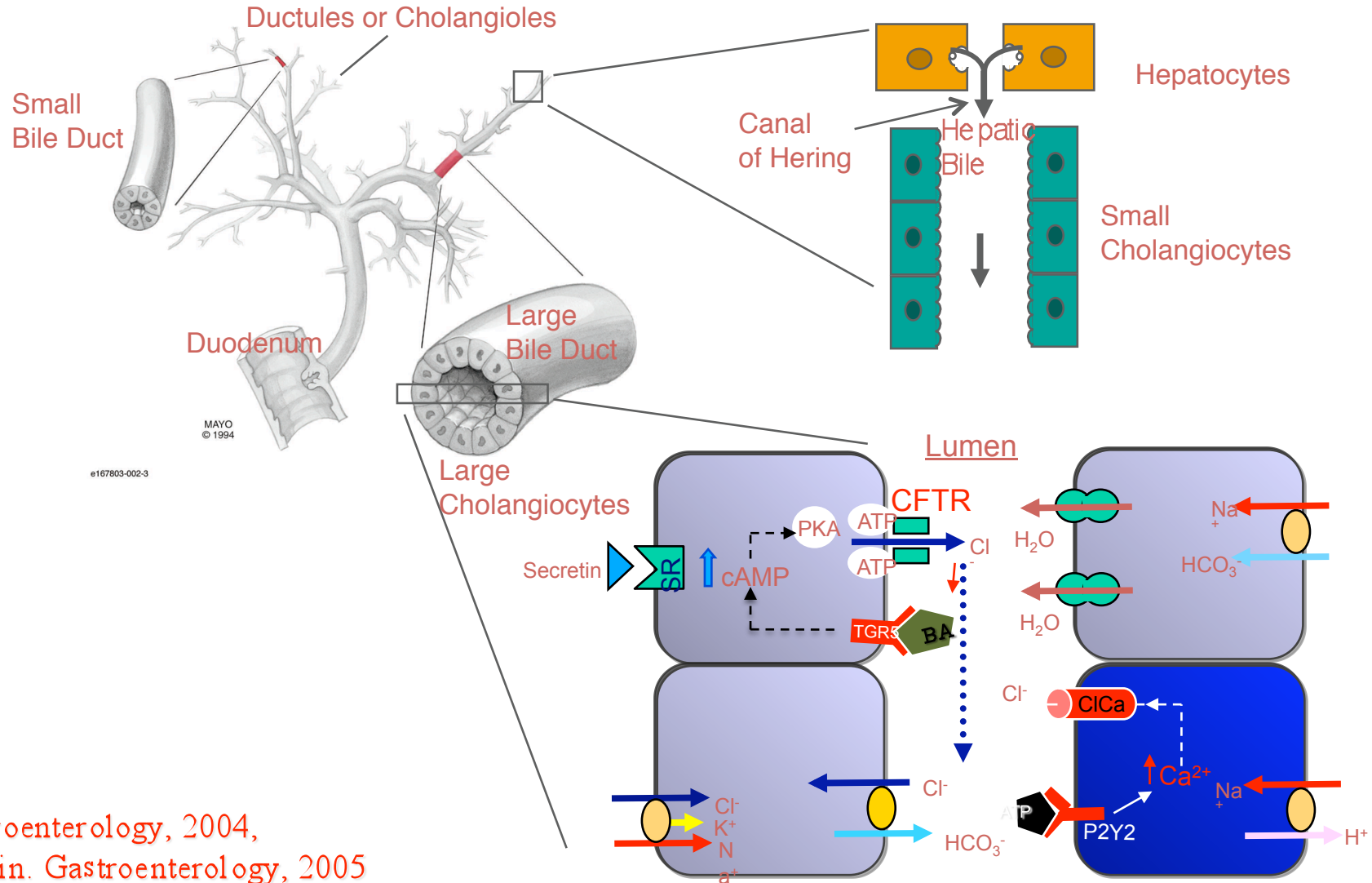
PSC stage IV



# Biology of cholangiocytes

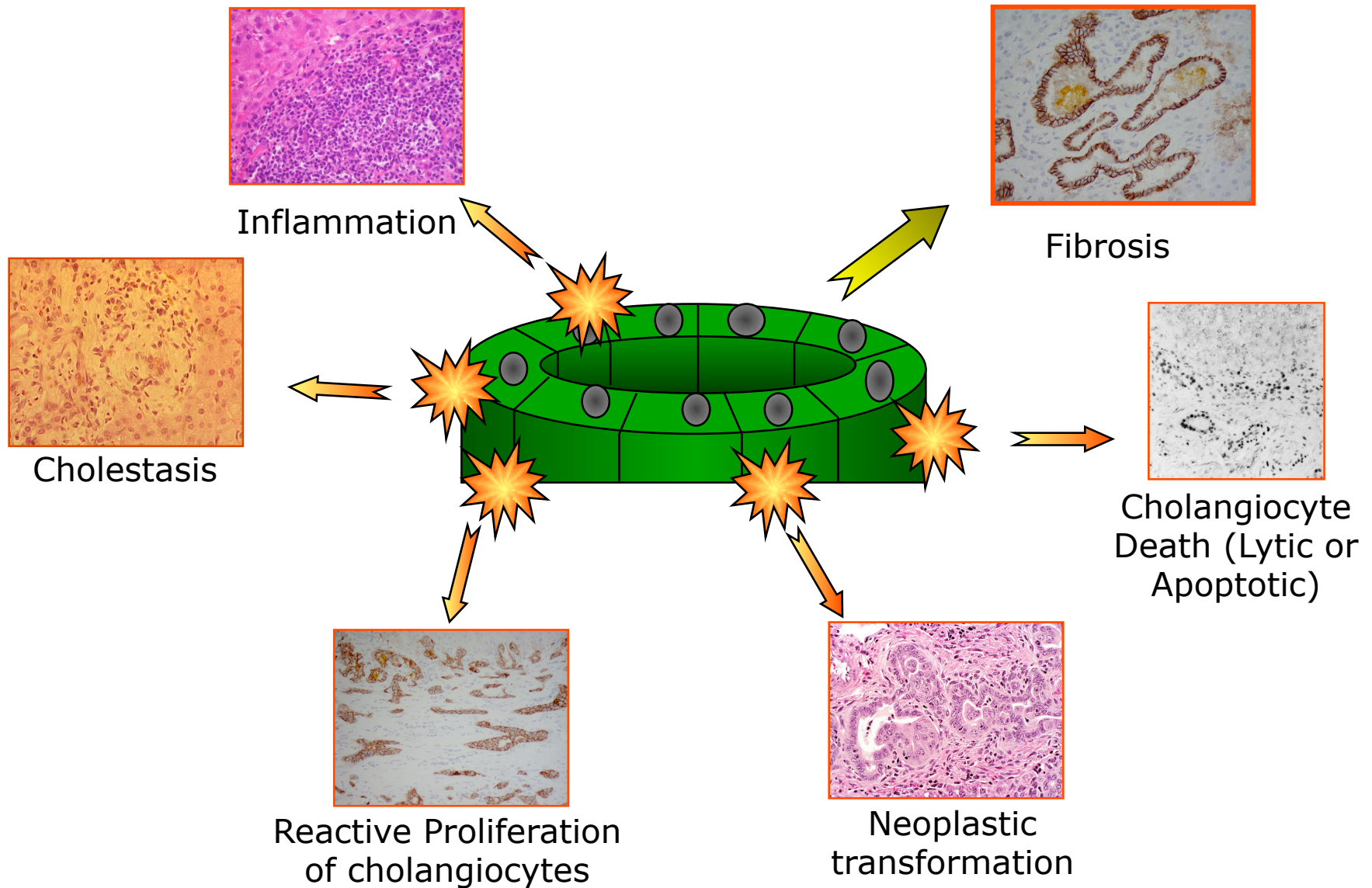


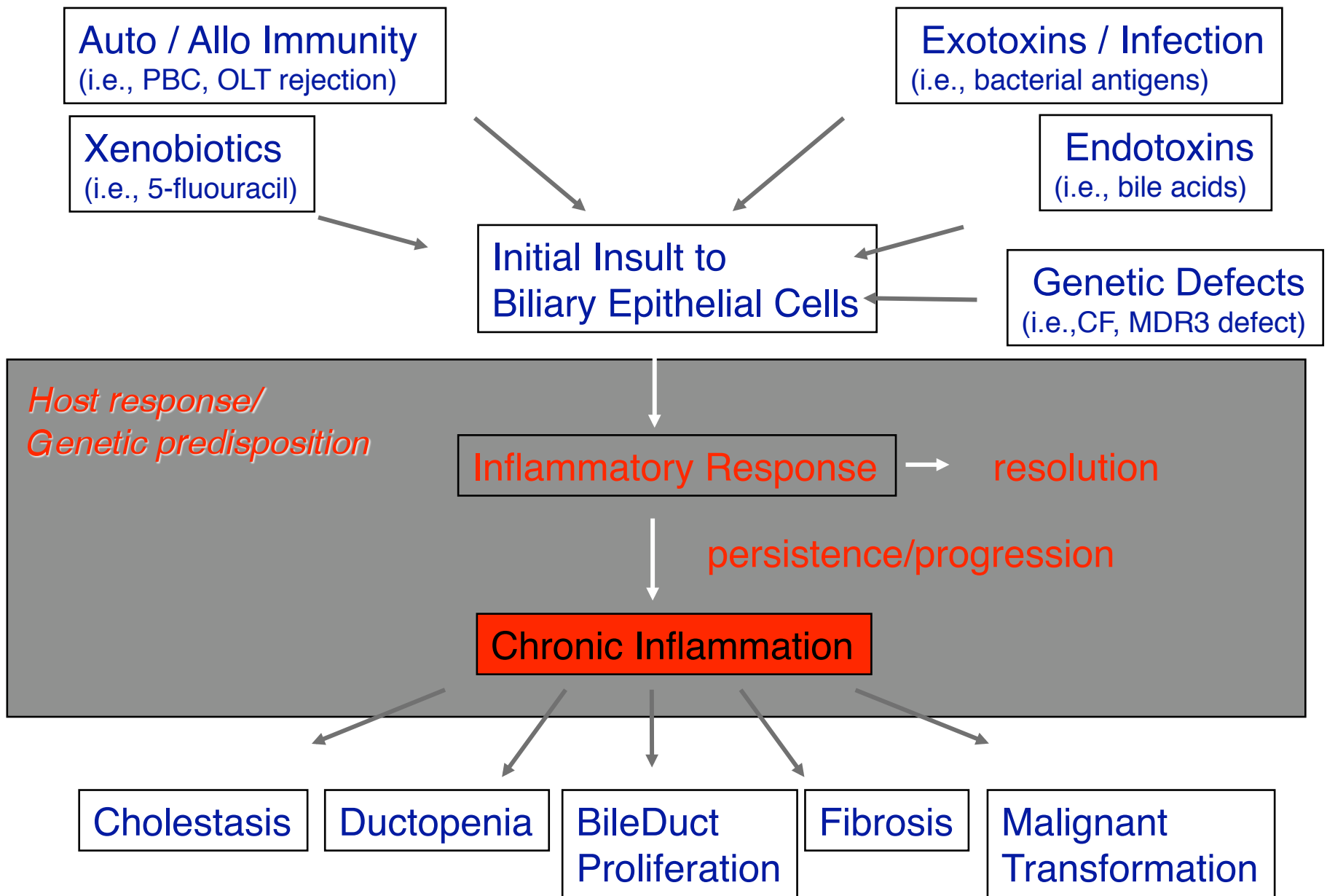
# PHYSIOLOGY OF THE BILIARY EPITHELIUM



Gastroenterology, 2004,  
 J. Clin. Gastroenterology, 2005

# Cholangiopathies result from the epithelial reaction to liver damage and its repair/regeneration attempts

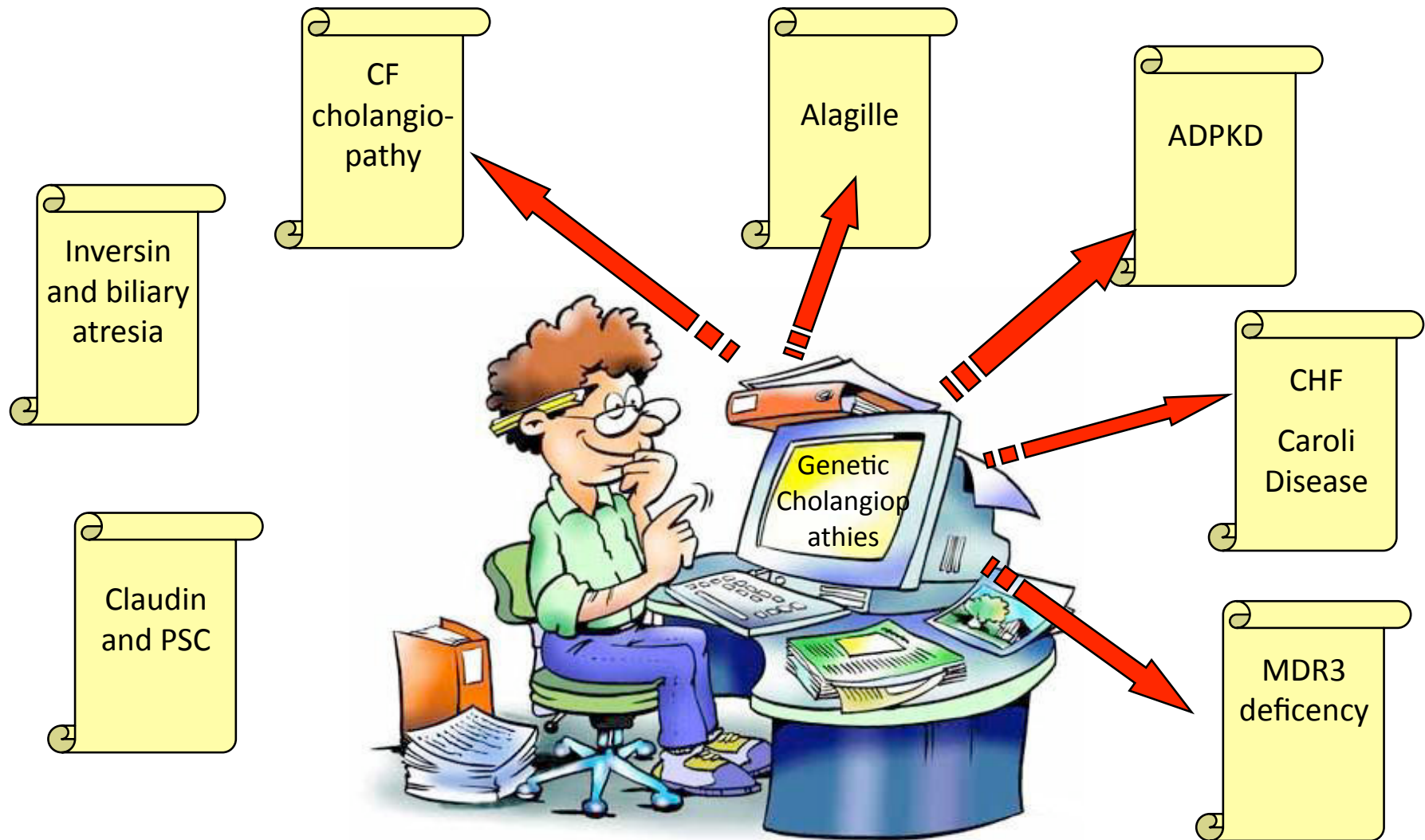






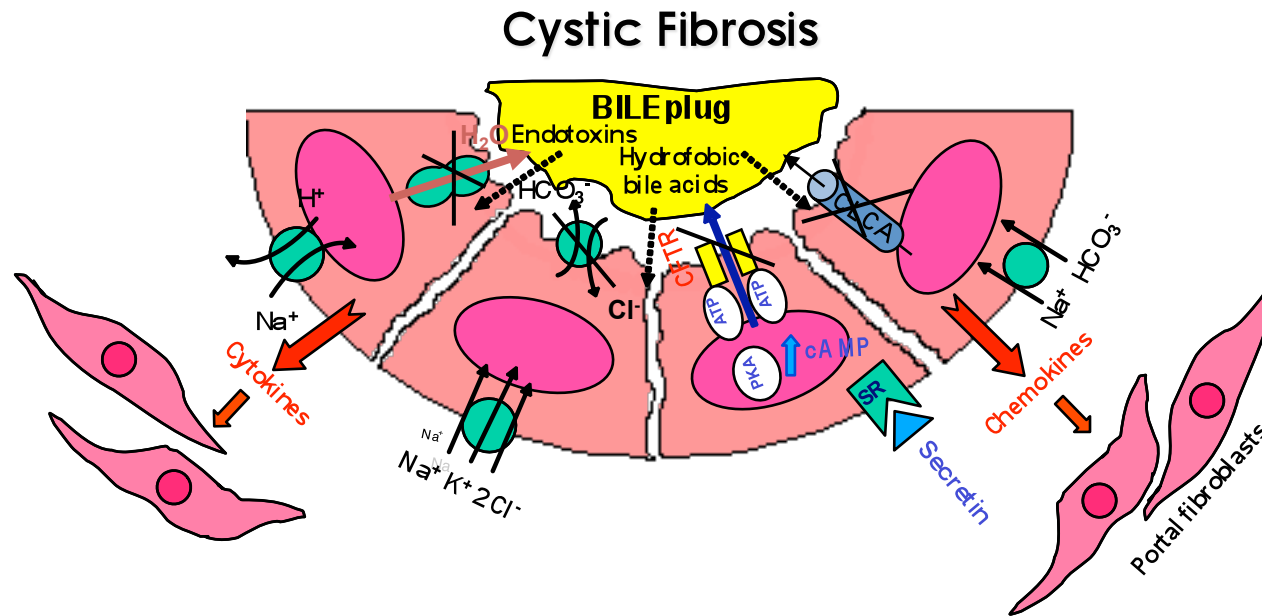
# Genetic Cholangiopathies are the Rosetta Stone

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# Cystic Fibrosis- causes a progressive sclerosing cholangiopathy in a subset of patients

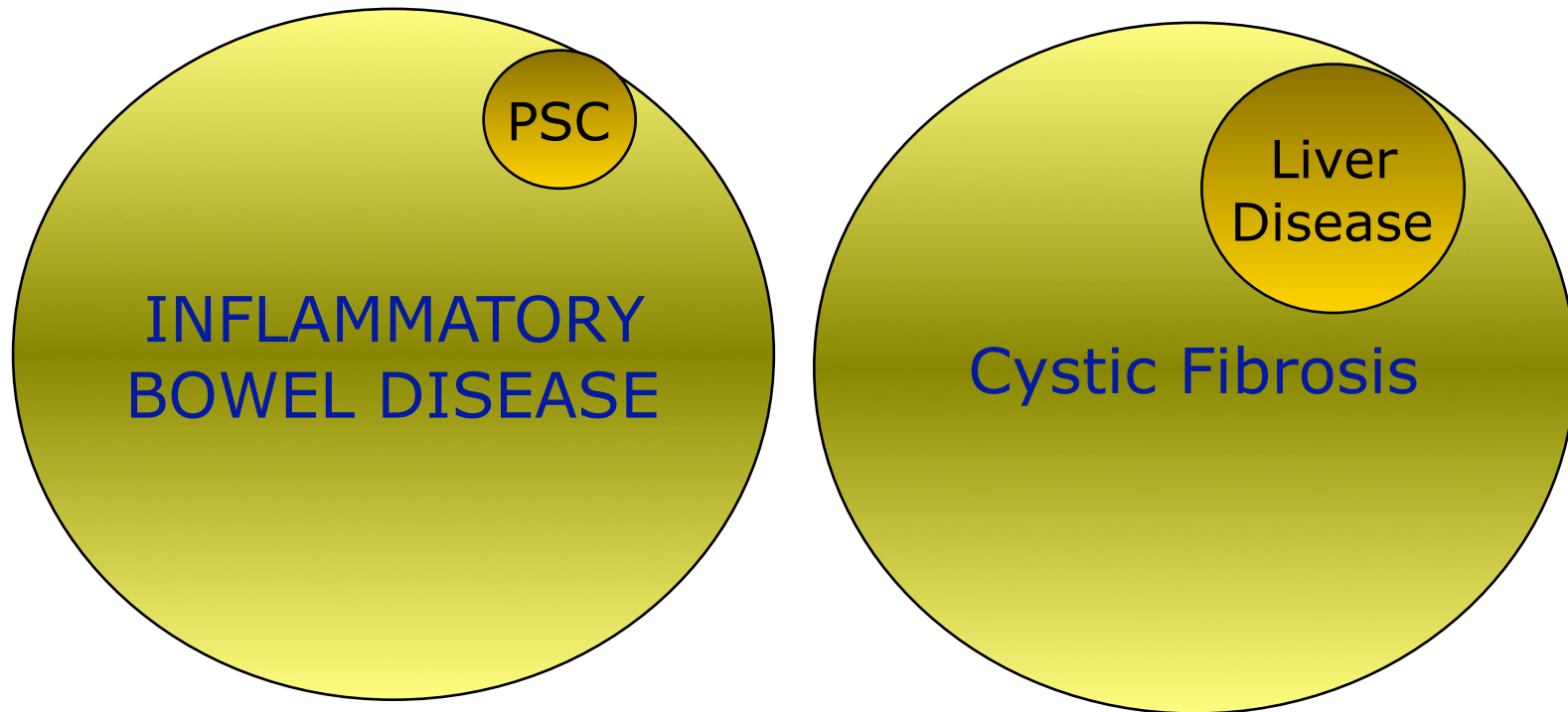
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Chronic cholestasis predisposes the biliary epithelium to damages

# Fibrosing cholangiopathies in Systemic conditions

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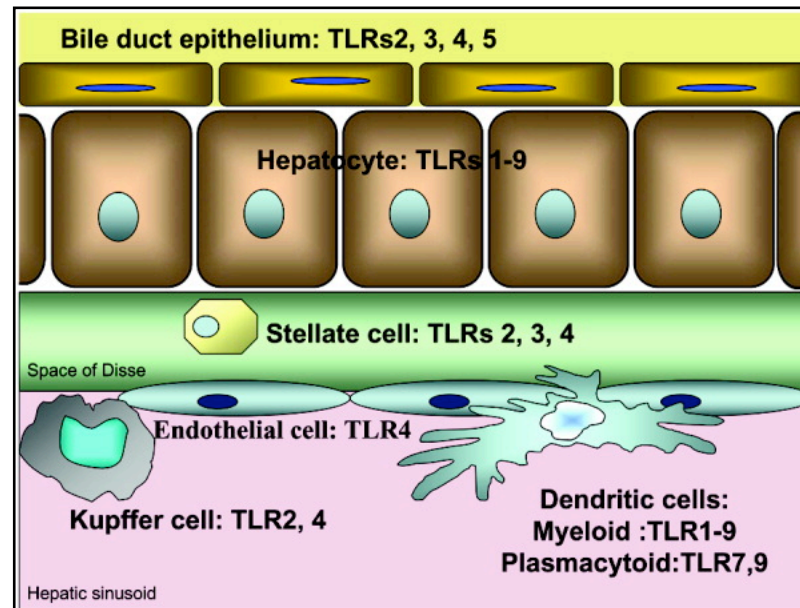
A two hit phenomenon?

# Altered Innate Immunity Response of the Biliary Epithelium to portal endotoxins cause biliary disease in Cystic Fibrosis

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- CFTR-KO mice possess the bile secretory defect of Cystic Fibrosis, but do not develop liver disease
- Experimental colitis generates liver disease in CFTR-KO mice, but not in their normal littermate
- Liver disease caused by colitis in CFTR-KO animals does not improve when bile secretion is restored using therapeutic bile acids
- Cholangiocytes isolated from CFTR-KO mice present an exaggerated inflammatory response to endotoxin
- Toll like receptor-4 pathway is activated with loss of the normal endotoxin tolerance

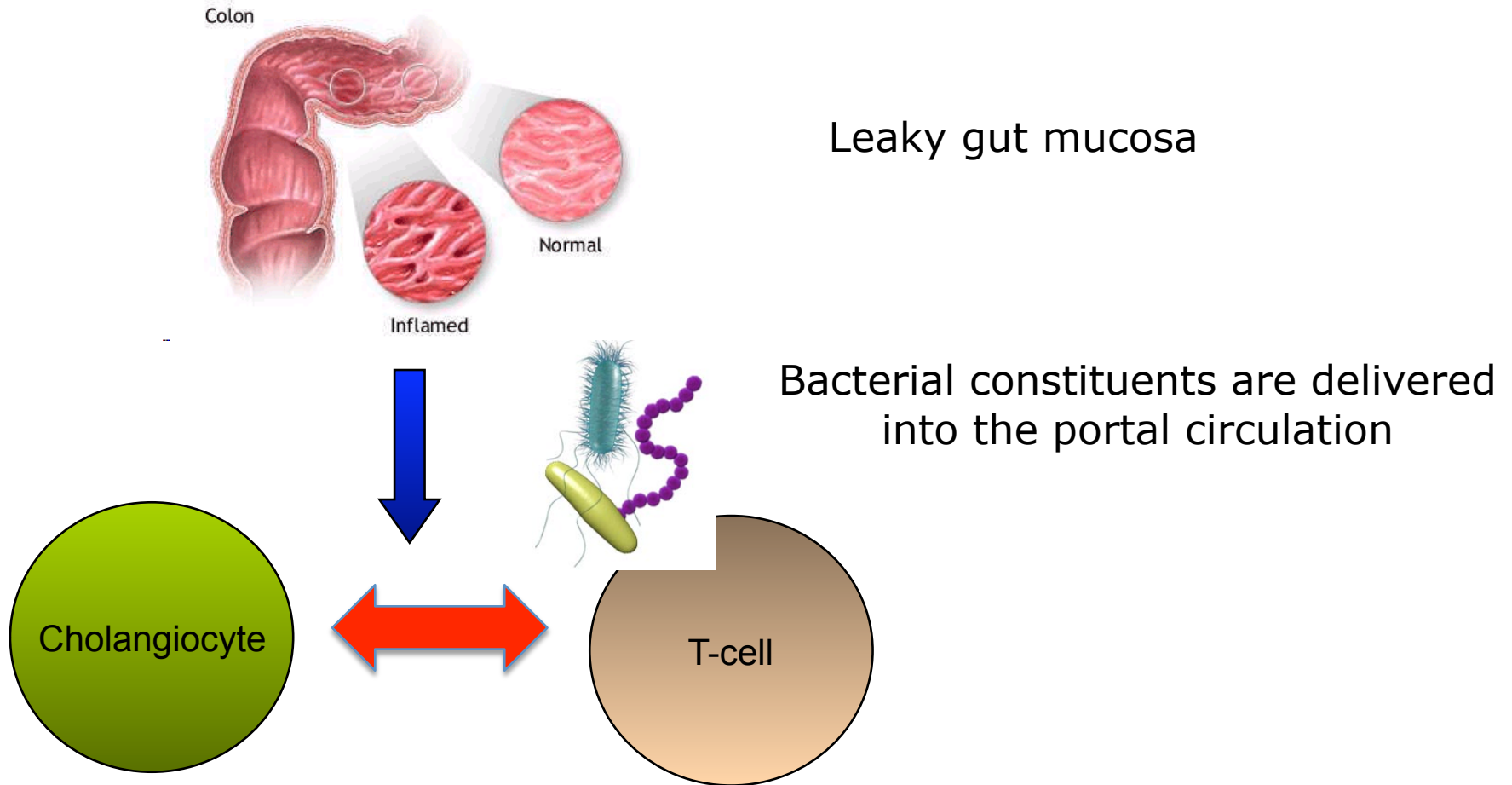
# Biliary epithelium protects against pathogens by expressing Toll-like receptors (TLRs)



(Szabo G. et al.,  
*Hepatology* 2006)

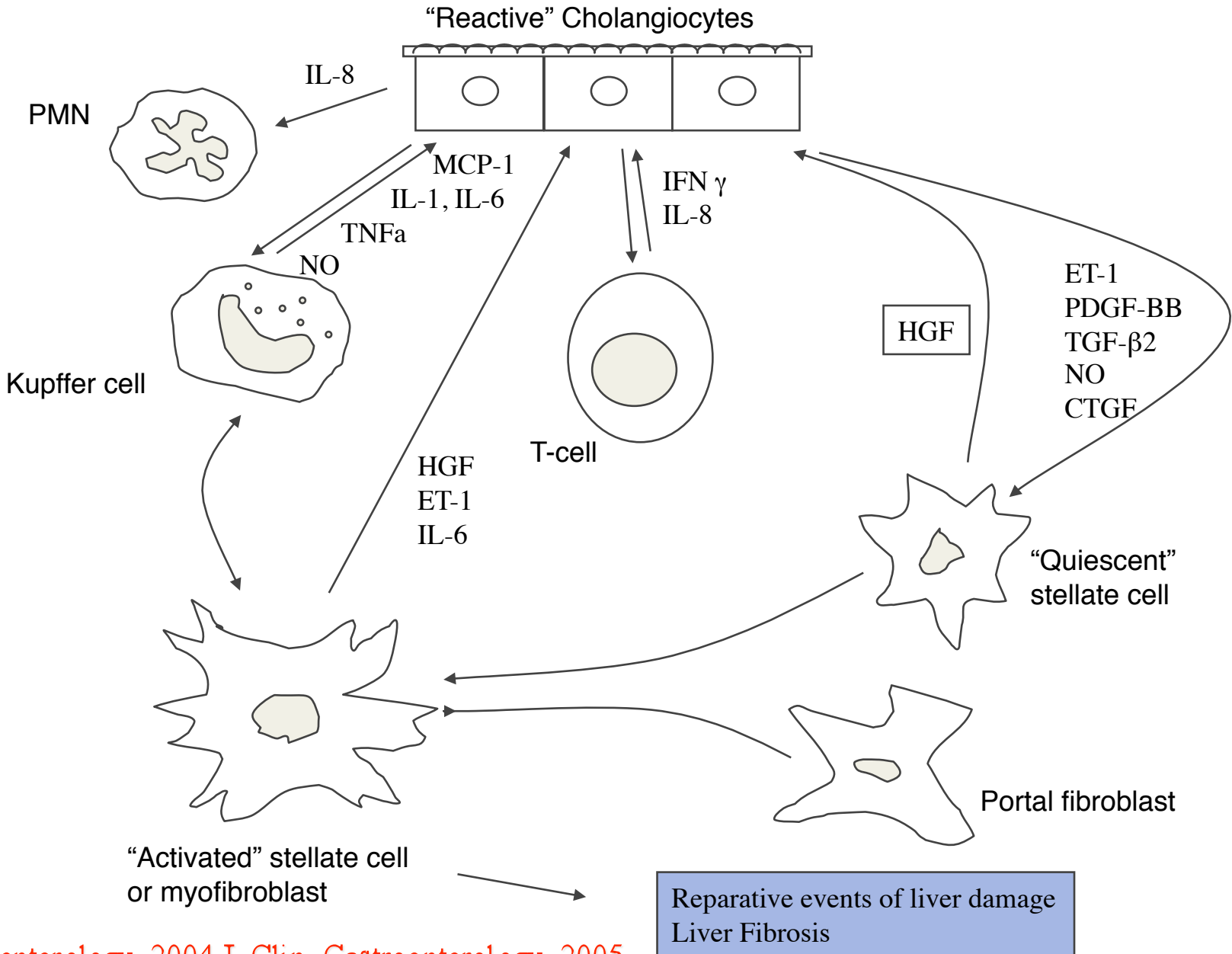
- ✓ TLRs belong to a family of protein that recognize and discriminate between specific patterns of microbial components (i.e. LPS, DNA, RNA, flagellin)
- ✓ In normal conditions a process of “**endotoxin tolerance**” prevents excessive inflammation
- ✓ IN Cystic Fibrosis, CFTR deficiency causes a loss of endotoxin tolerance and in the presence of a “second hit”, such as colitis, the dysregulated inflammatory response causes liver disease

# Hypothesis: a “second hit” may in part explain of PSC pathogenesis



An inflammatory response is triggered in conditions where endotoxin tolerance is decreased because of a cholangiocyte dysfunction (such as CFTR deficiency, or TGR5 or Glypican 6 , etc)

# Cellular Cross-talk in Cholangiopathies

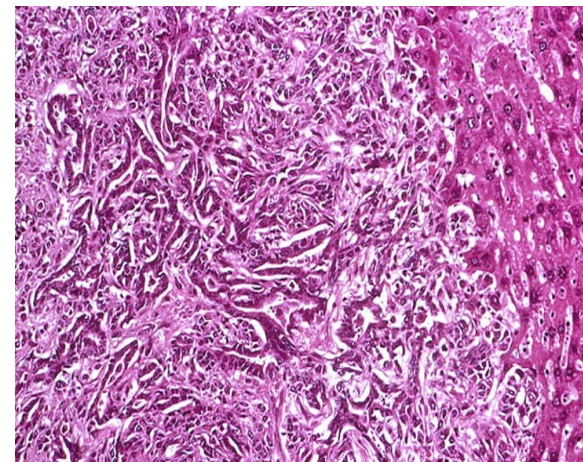
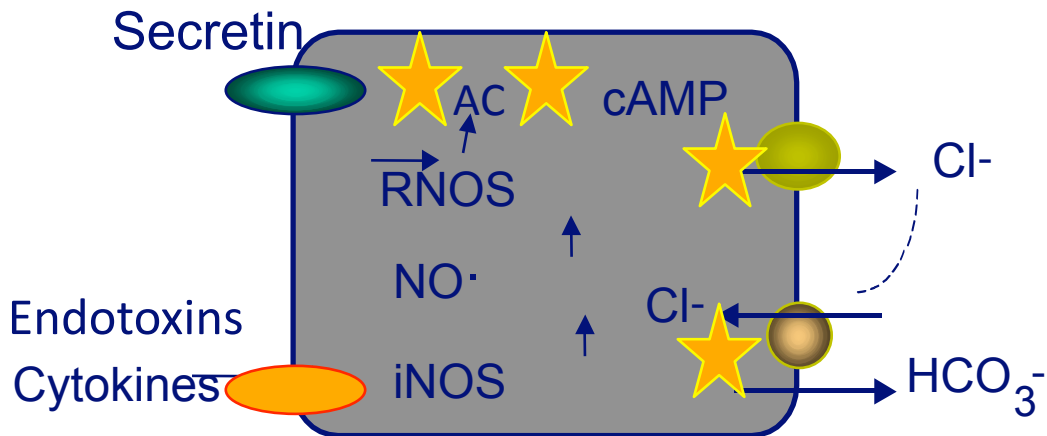
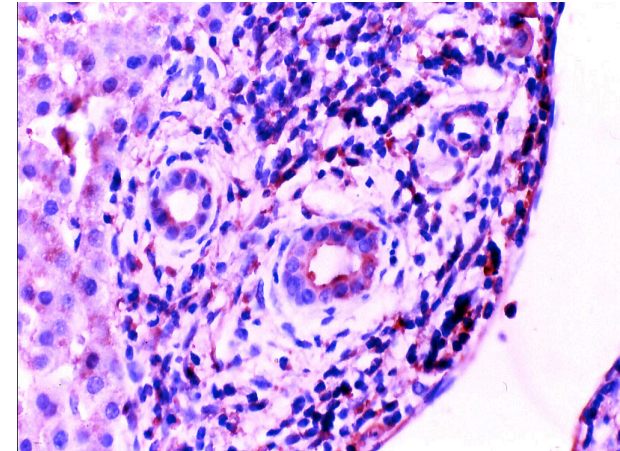
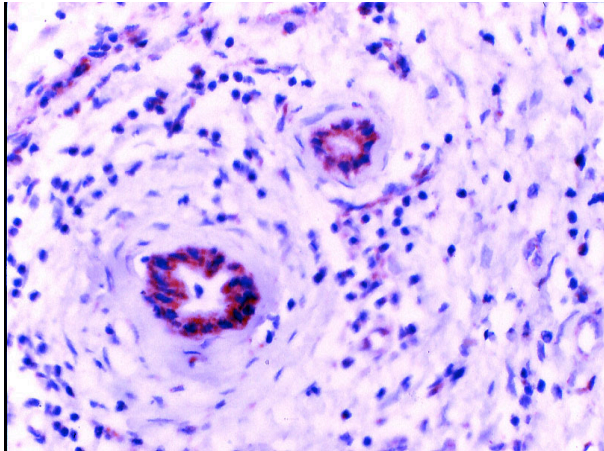


Gastroenterology, 2004 J. Clin. Gastroenterology, 2005

# Cholangiocyte iNOS and Nitrotyrosine are increased in Primary Sclerosing Cholangitis

iNOS

3-Nitrotyrosine





# PSC Partners Seeking a Care

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“For all those whose care is our concern, the work goes on, the cause endures, the hope is real, and the dream shall come true”

Modified from Edward Kennedy, 1980