GI Pathophysiology

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Ongoing projects

• The role of bile acids in GI carcinogenesis prevention and treatment

• Gut-liver axis and liver regeneration
Study targets

- **Molecule: nuclear receptors**
- **Organ Sites: Liver and intestine**  
  *(gut-liver axis)*
- **Chemicals: Bile Acids, Retinoic Acid**
# Nuclear receptor subfamily (based on ligands)

## Endocrine receptors
- AR: Androgen
- ER: Estrogen
- GR: Glucocorticoid
- MR: Mineralcorticoid
- PR: Progesterone

## Adopted orphan receptors
- RARs: all trans-RA
- RXRs: 9 cis-RA
- VDR: Vitamin D3
- TR: Thyroxine T4
- CAR: Androstanide
- Rodent PXR PCN
- Human PXR: Rifampicin
- ERR: Diethylstilbestrol
- FXR: Bile acids
- HNF4: Fatty acids
- LXR: Oxysterol
- PPARα: Fatty acids
- PPARγ: 15d-PGJ2
- PPARδ: cPG1
- RORs: Cholesterol/melatonin
- SF-1: Phospholipids

## Orphan receptors
- COUP-TFs
- GCNF (germ cell nuclear factor)
- NOR1 (RA receptor-related protein)
- NURR1 (Nur-related protein)
- NUR77 (TR3, NGF1-B)
- PNR (photoreceptor cell-specific nuclear receptor)
- Rev-erb alpha and beta
- TLX (tailless homolog)
- TR2, 4 (testicular receptor)
Gut-liver Axis

3. Reabsorbed bile salts are recycled by enterohepatic circulation.

4. 5% of bile salts are lost in feces.

KEY: = Enterohepatic circulation of bile salts

1. Secreted bile salts consist of 95% old, recycled bile salts and 5% newly synthesized bile salts.

2. 95% of bile salts are reabsorbed by the small intestine.

Cholesterol

Liver

Bile salts

Common bile duct

Gallbladder

Stomach

Sphincter of Oddi

Duodenum

Hepatic portal vein

Terminal ileum

Colon

Bile salts hydrolase

7α-dehydroxylase

DCA and LCA

CA and CDCA
Dysregulated bile acid homeostasis can be considered a common etiological factor for GI disease and cancer

- Obesity: Elevated levels of toxic bile acids are presented in obese people, who have increased risk of GI cancer.
- Viral infections: Bile acids play a role during the pathogenesis of HCV infections by promoting HCV replication and HBV viral gene expression. Serum bile acid levels predict the severity of HCV and the success of interferon α treatment in HCV and HBV patients.
- Chemical carcinogenesis: Ethanol increases the synthesis of toxic bile acids, and aflatoxin B1 induces cholestasis by excreting into bile.
- Immunity: Bile acids modulate inflammation and innate immunity.
- Autoimmune disease: Bile acid homeostasis is disrupted in primary biliary cirrhosis and primary sclerosing cholangitis.
- All aforementioned diseases are associated with GI cancer.
Bile acid receptor FXR knockout mice develop spontaneous liver cancers
DCA and LCA induce the expression of DNA repair genes and damage DNA.

**HCT116 (16 h)**

- ATM
- LIG4 (Fold induction vs. DMSO)
- TP53

**Huh7 (48 h)**

- ATM
- LIG4
- TP53

% of cells with tails

- DMSO
- DCA (150 μM)
- LCA (20 μM)

**Significance:**

- * indicates statistical significance.
DCA and LCA induce DNA damage in mouse primary hepatocyte
DCA and LCA induce the expression of TNFα and NFkB in HCT116 and Huh7 cells
LCA increases the expression and nuclear export of Nur77 in apoptotic HCT116 cells
Liver regeneration is delayed in hepatocyte RXRα-deficient mouse livers.
Liver regeneration is impaired when liver is fatty

**Cyclin D**

![Graph showing relative mRNA levels for control and Western diets at different time points: Control, 1 Day, 1.5 Day, 2 Day, and 3 Day. The graph indicates significant differences marked with asterisks (*) between control and Western diets at these time points.](image-url)