Pečeň a zápalové črevné choroby

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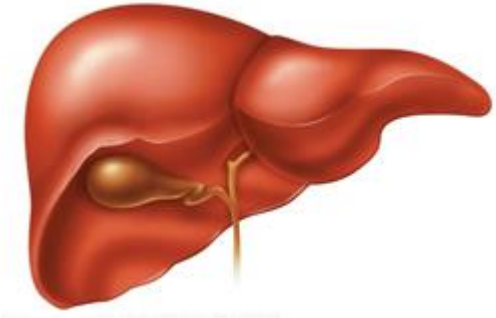
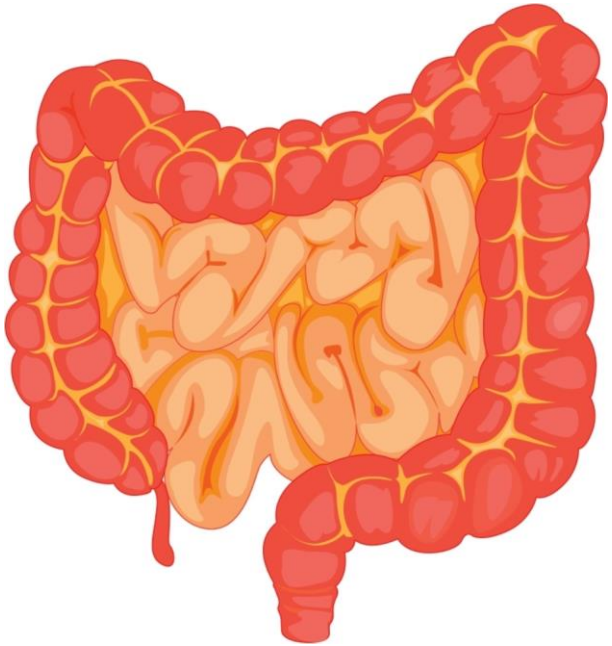
Kľúčové slová





Mikroflóra a imunitná reakcia v pečeni

- Ak je zdravé črevo, pečeň je sterilná
- Pečeň ako druhá obranná línia po prieniku baktérií do cirkulácie
- Nie len baktérie, ale aj bakteriálne produkty – LPS, bakteriálna DNA
- Aktivácia Kupferových buniek, inflamazómov
- Systémový zápal
- Poškodenie ďalších orgánov – mozog, pľúca, pankreas

Gut-liver crosstalk v systémovom zápale

Table 1 Gut-liver crosstalk in systemic inflammation

Major finding	Study type	Reference
Bacteremia due to bacterial translocation is associated with an increased risk of bacterial peritonitis	Human	[51]
Hepatic encephalopathy is associated with changes in the intestinal microbiota	Human	[52]
Acute liver rejection is associated with changes in intestinal microbiota, loss of gut barrier, and enhanced systemic inflammation	Rodent	[55, 56]
CX3CR1 signaling by intestinal macrophages regulates steatohepatitis	Rodent	[58]
A hepatic vascular and phagocytic network functions as a "secondary firewall" to filter escaped gut commensals	Rodent	[60]
Liver cirrhosis is associated with increased inflammasome activation in ascitic fluid macrophages	Human	[61]
Translocation of bacterial DNA in liver cirrhosis is associated with enhanced systemic inflammatory activity	Human	[62, 63]
Hepatic STAT3 signaling protects against systemic inflammation caused by polymicrobial sepsis	Rodent	[72]
Hepatic gp130-STAT3 signaling induces myeloid-derived suppressor cells that protect against polymicrobial sepsis	Rodent	[73]
Hepatic STAT3 signaling regulates cellular and humoral pulmonary immunity against bacterial infection	Rodent	[74]
The liver enhances and protects against systemic inflammation through Kupffer cell-mediated cytokine production and detoxification by parenchymal cells, respectively	Rodent	[76]
Kupffer cells aggravate lung damage in acute pancreatitis	Rodent	[78, 79]

Summary of key studies that addressed the bidirectional gut–liver crosstalk in the pathogenesis of systemic inflammation. The type of study (animal model or human) is indicated
STAT3 signal transducer and activator of transcription 3

de Jong et al., Critical Care, 2016

Črevo ➡ pečeň

- IBD
- Spoločná patogenéza s pečeňovými chorobami
- Dysbióza
- **Zvýšená črevná permeabilita**
- Translokované baktérie vstupujú do pečene
- Aktivované lymfocyty z čreva vstupujú do pečene a prispievajú k jej patológii

Pečeň ➡ črevo

- Cirhóza
- Zvýšená črevná permeabilita
  - Priamy účinok primárnej patológie (alkohol)
  - Zápalové mediátory produkované aktivovanou imunitou
  - Obštrukcia v žlčových cestách – črevná dysbióza
- Translokácia bakteriálnych komponentov z čreva do cirkulácie
- Zápal bez infekcie
- Acute-on-chronic liver failure
- Zvýšená mortalita

Porušená črevná bariéra - príčiny

- Hypoperfúzia čreva
- Infekcia
- Toxíny
- Liečivá
- Nutrienty
- Ostatné environmentálne faktory

Porušená črevná bariéra - choroby

- IBD
- Celiakia
- Syndróm dráždivého čreva
- Potravinové alergie
- Kritické stavy
- Metabolické choroby
- Obezita

Porušená črevná bariéra - IBD

- Jedna z prvých udalostí ešte pred klinickou manifestáciou

Table 4 Means for the assessment of intestinal permeability (functional tests, bacteria-related tests)

Means	*Hu*	*An*	*Test molecules*	*Test site*	*Material needed*	*Disadvantages*
Ex vivo						
Ussing chamber	x	x	H_2O, ions, sugars etc.,	site specific	biopsies	invasive
In vivo – permeability assays						
Lactulose/mannitol	x	x	oligosaccharides of different MW	small intestine	urine	time consuming
Sucralose	x	(x)	sucralose(comb.)*	colon	urine	time consuming
Sucrose	x	(x)	sucrose(comb.)*	stomach	urine	time consuming
PEG4000/400	x	(x)	polyethylene glycols	whole intestine	urine	time consuming
51Cr-EDTA	x	x	51Cr-EDTA	whole intestine	urine	radio-activity
In vivo – bacteria-related						
LAL assay	x	x	endotoxin (LPS)	whole intestine	plasma	assay limitation
EndoCAb	x	x	anti-LPS antibodies	whole intestine	serum	only in acute phase
D-lactate	x	x	bacterial lactate	whole intestine	plasma	low specificity
Butyrate production	x	x	BPB (PCR)	colon	feces	special labs, limited data
Hemolysin test	x	x	pathogens (cell culture)	colon	feces	special labs, limited data
Inner colon mucus	x	x	quantification of bacteria	colon	biopsies	invasive,limited standardization
Liver steatosis	x	x	fat content in the liver	whole intestine	MRT, US	expensive unspecific
Breath tests	x	x	fat content in the liver	whole intestine	GC/MS	unclear specificity

Table 5 Means for the assessment of intestinal permeability (biomarkers, histology)

Means	*Hu*	*An*	*Test molecules*	*Test site*	*Material needed*	*Disadvantages*
In vivo – biomarkers of epithelial cell damage						
Citrulline	x	x	endogenous ep product	small intestine	plasma	
FABP	x	x	endogenous ep marker	site- specific	plasma	only in acute phase?
αGST	x	x	endogenous ep enzyme	n.a.	plasma, urine	only in acute phase?
Claudin-3	x	x	ep tight junction protein	n.a.	urine	limited data
In vivo – other biomarkers						
Fecal calprotectin	x	(x)	neutrophil release product	colon	feces	unspecific marker of gut inflammation
α1-anti- trypsin test	x	(x)	endogenous amino acid	small intestine	feces/ serum	unclear specificity
sIgA	x	x	IgA (ELISA)	whole intestine	serum	low specificity
In vivo – histological approaches						
Tight junction expression	x	x	RNA (qPCR), Western blot	site- specific	biopsies	invasive
Goblet cell analysis	x	x	histology	site- specific	biopsies	invasive
Shedding of epithelium	x	x	histology	site- specific	biopsies	invasive
Paneth cell loss**	x	x	histology	site- specific	biopsies	invasive
Defensins			RNA (qPCR), Western blot	site- specific	biopsies	invasive
Mucus analysis***			histology/ staining	site- specific	biopsies	invasive

Následky v pečeni

- MAMP – microbe-associated molecular patterns
- PRRs – pattern recognition receptors
  - LPS – TLR4
  - Flagellin – TLR5
  - dsRNA – TLR3
  - Unmethylated CpG – TLR9
- Produkcia zápalových cytokínov
- Prozápalový fenotyp
- Poškodenie pečene

SCIENTIFIC REPORTS

OPEN

Total fecal microbiota transplantation alleviates high-fat diet-induced steatohepatitis in mice via beneficial regulation of gut microbiota

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Da Zhou, Qin Pan, Feng Shen, Hai-xia Cao, Wen-jin Ding, Yuan-wen Chen & Jian-gao Fan

DNA ako marker aktivity choroby

- Extracelulárna DNA v cirkulácii
  - Nukleárna
  - Mitochondriálna
  - Bakteriálna

- Bakteriálna DNA v pečeni
  - Gén pre 16S rRNA

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