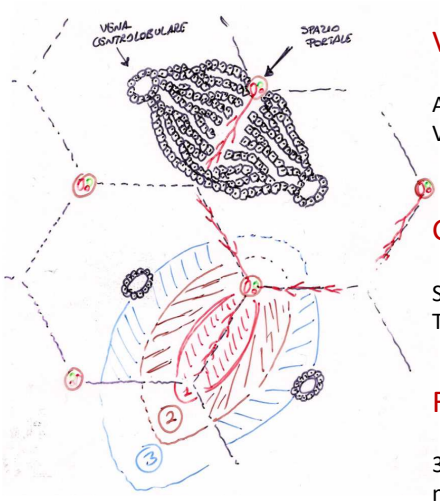

Vascolarizzazione

Arteria epatica ≈ 400 ml/min
Vena porta ≈ 1000 ml/min

Gradiente pressorio

Sovraepatiche ≈ 0 mm Hg
Tronco portale ≈ 9 mm Hg

Flusso linfatico

30-50 % della linfa si forma nel fegato

0163-769X/07/$20.00/0
Printed in U.S.A.

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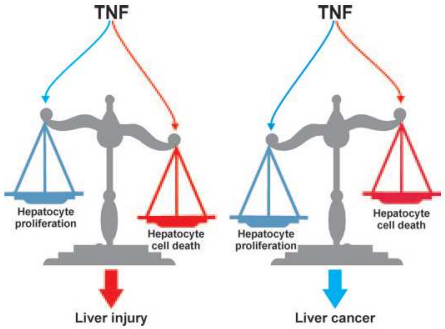
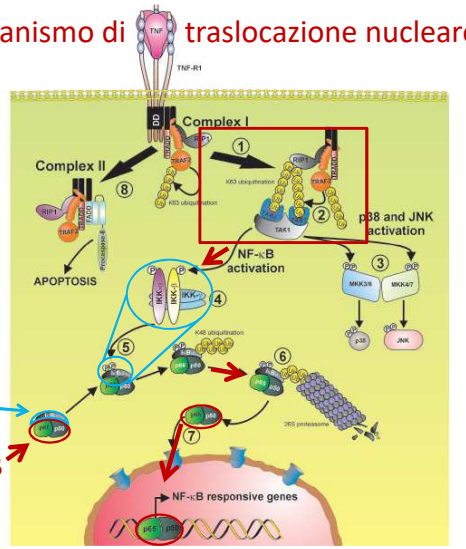
Hepatic Tumor Necrosis Factor Signaling and Nuclear Factor-κB: Effects on Liver Homeostasis and Beyond

Andy Wullaert, Geert van Loo, Karen Heyninck, and Rudi Beyaert

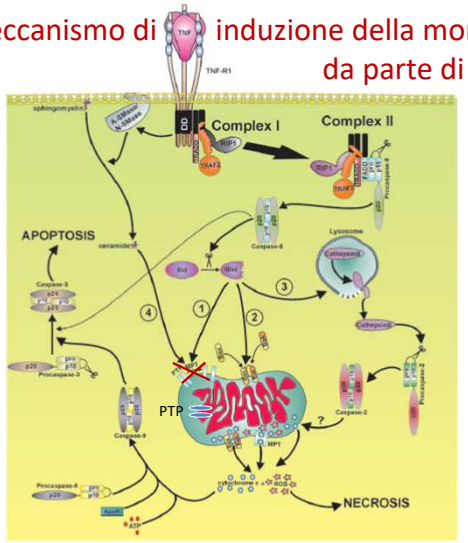
Unit of Molecular Signal Transduction in Inflammation, Department for Molecular Biomedical Research-VIB, and Department of Molecular Biology, Ghent University, Technologiepark 927, B-9052 Ghent (Zwijnaarde), Belgium



Meccanismo di traslocazione nucleare di NF-κB



Meccanismo di induzione della morte cellulare da parte di TNFα



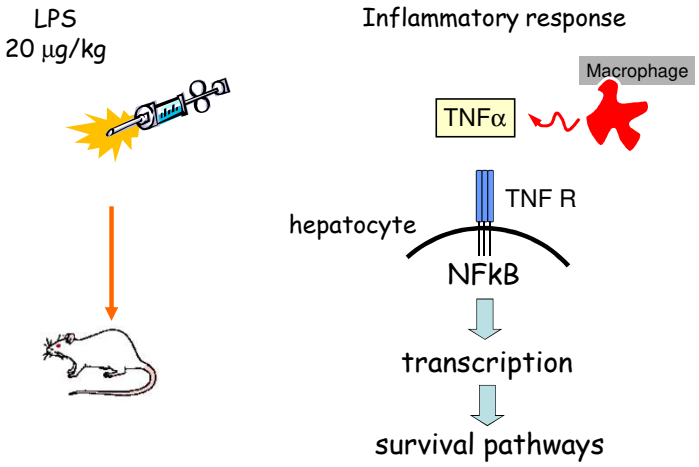
Proc. Natl. Acad. Sci. USA
Vol. 76, No. 11, pp. 5939–5943, November 1979
Medical Sciences

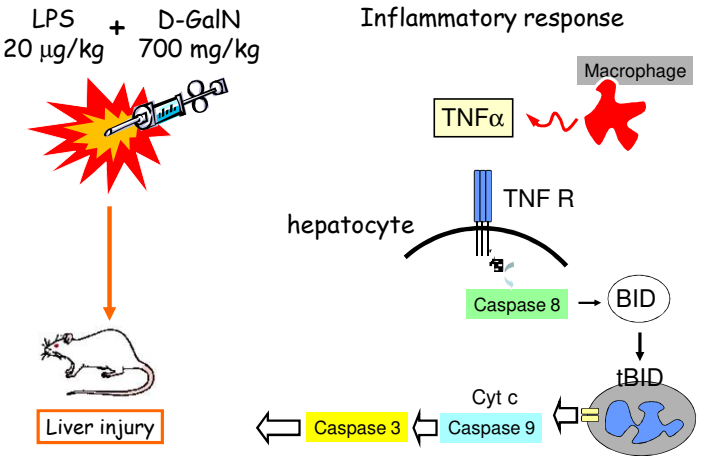
Galactosamine-induced sensitization to the lethal effects of endotoxin

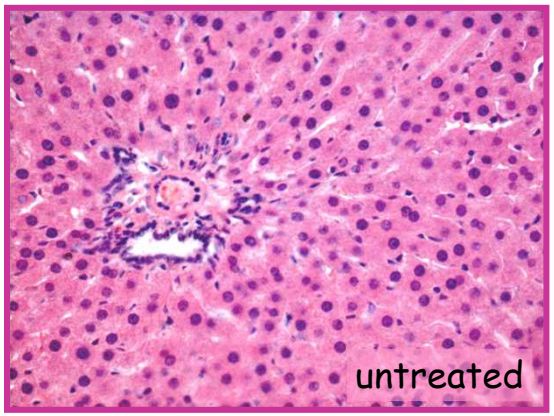
(lipopolysaccharide/liver modification/enhanced toxicity)

CHRIS GALANOS*, MARINA A. FREUDENBERG*, AND WERNER REUTTER†

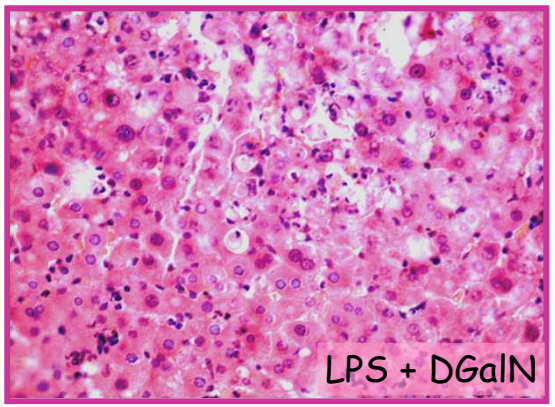
ABSTRACT Treatment of rabbits, rats, and mice with D-galactosamine increased their sensitivity to the lethal effects of lipopolysaccharide several thousand fold. The susceptibility of the animals was highest when the lipopolysacharide was injected together with galactosamine and decreased successively when injection was carried out 1, 2, and 3 hr later. Sensitization was absent when the lipopolysaccharide was administered 1 hr before or 4 hr after galactosamine. The onset of lethality after treatment with galactosamine and lipopolysaccharide occurred faster than with lipopolysaccharide alone; usually all animals died 5–9 hr later. The galactosamine-induced sensitization to lipopolysaccharide could be reversed by uridine which is known to inhibit the early biochemical alterations induced by the amino sugar in the hepatocytes. Although galactosamine is known to exhibit hepatotoxic activity inducing ultimate necrosis of the hepatocytes, the data so far suggests that the sensitization to lipopolysaccharide is related only to the early metabolic effects of the hexosamine.





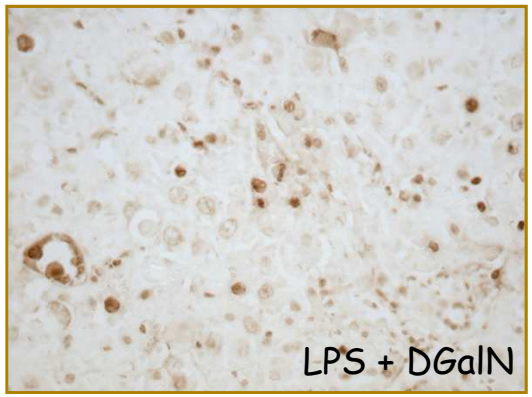


Soriano et al. (2004) J. Biol. Chem. 279, 36803



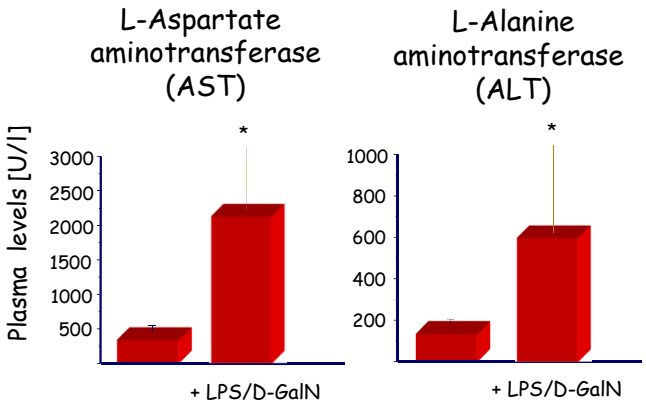
Soriano et al. (2004) J. Biol. Chem. 279, 36803

TUNEL staining



X 400

Soriano et al. (2004) J. Biol. Chem. 279, 36803



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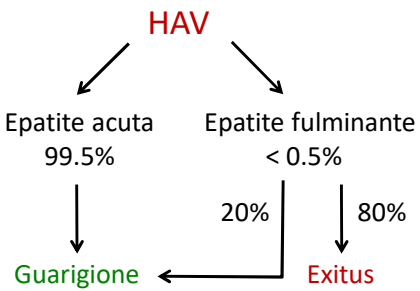
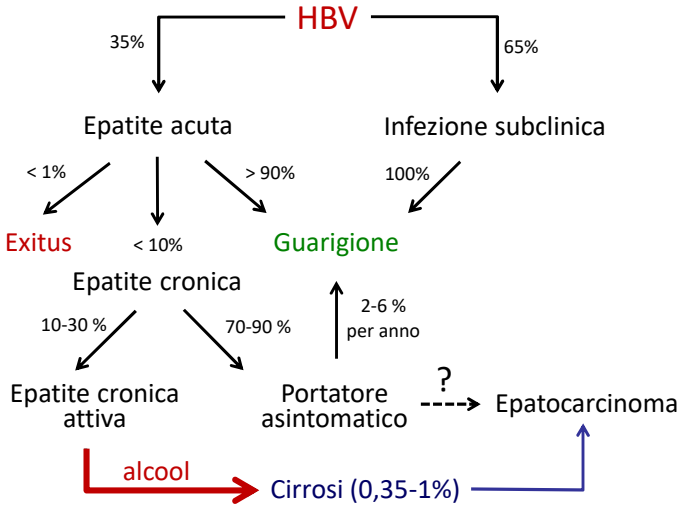
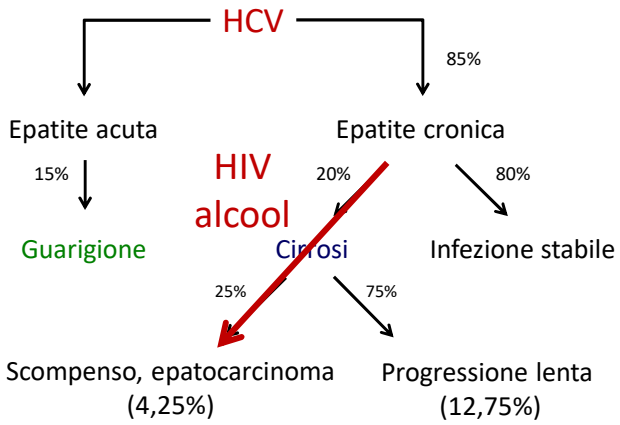


Non cronicizza mai



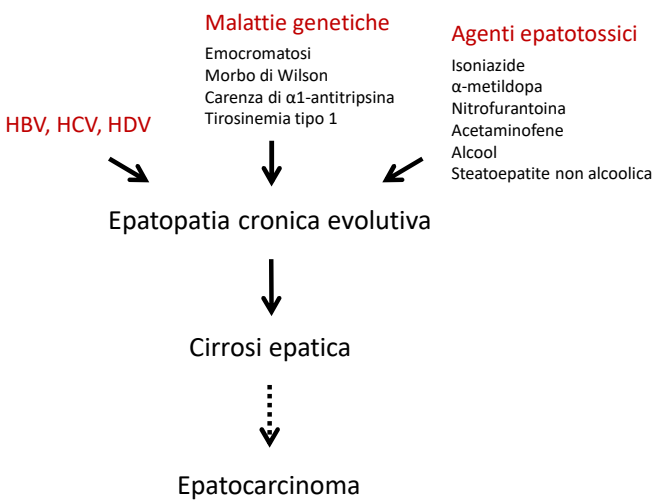


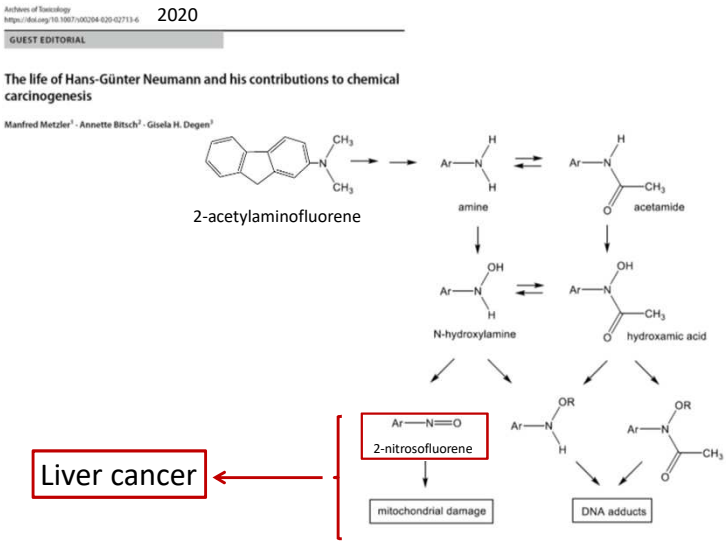
Patogeni causa di epatite

Virus dell'epatite A (HAV)
Virus dell'epatite B (HBV)
Virus dell'epatite C (HCV)
Virus dell'epatite D (HDV, coinfezione con HBV)
Virus dell'epatite E (HEV)

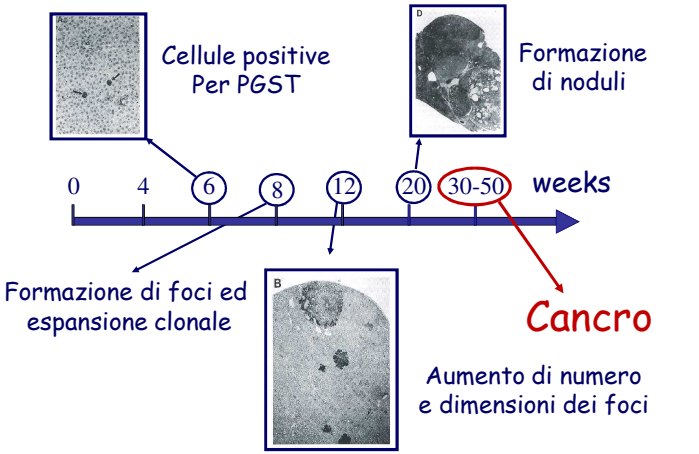
Virus della febbre gialla
Virus di Epstein-Barr (mononucleosi infettiva)
Virus di Lassa, Marburg ed Ebola
Virus della rubeola
Virus dell'Herpes Simplex (HSV)
Citomegalovirus
Enterovirus (oltre a HAV)

Leptospire
Entamoeba histolytica

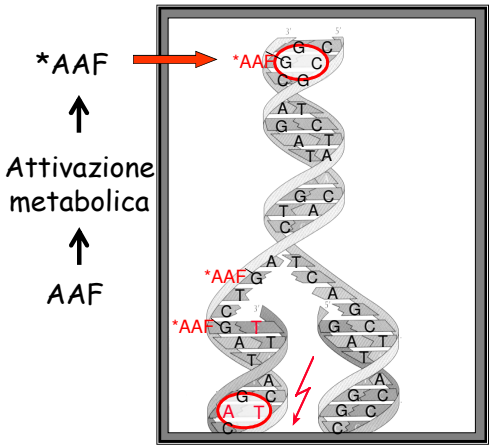




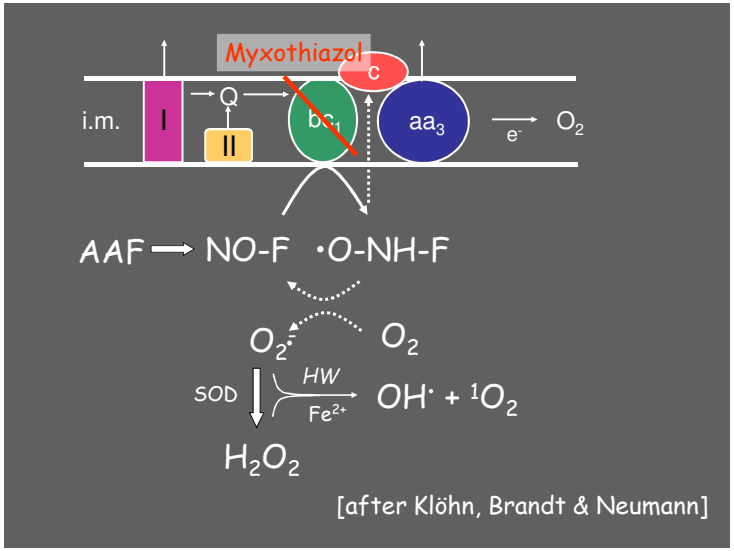
Epatocarcinogenesi da 2-acetilaminofluorene

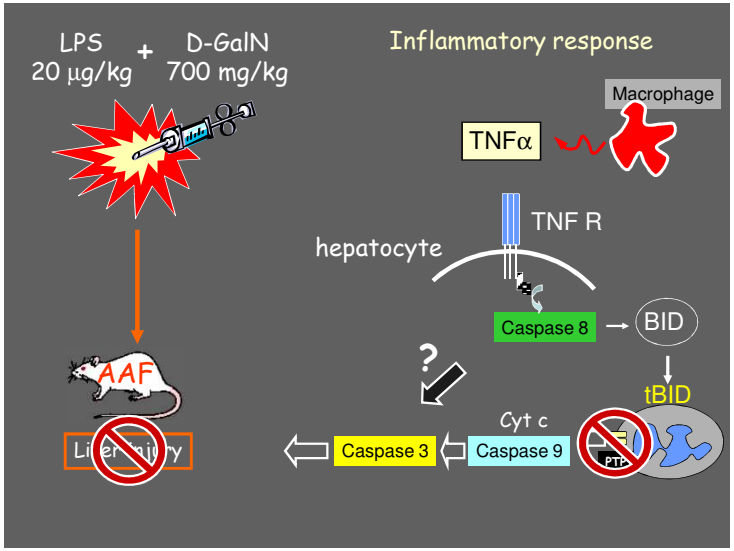


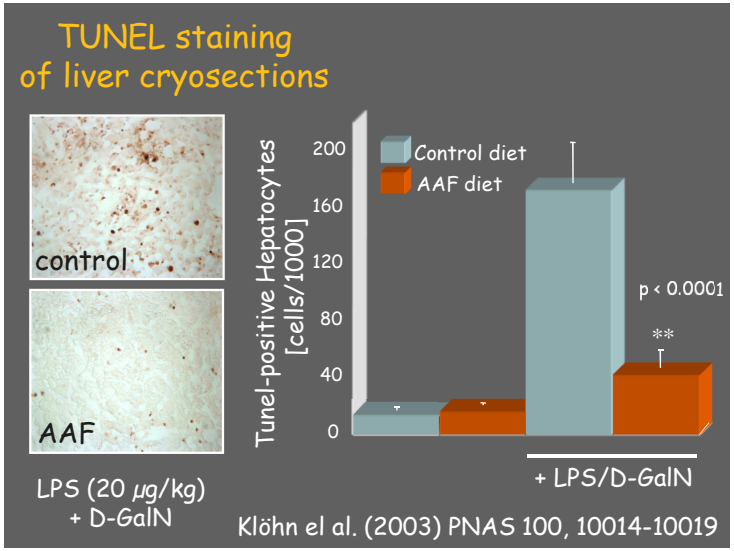
Meccanismo di mutazione indotta da AAF

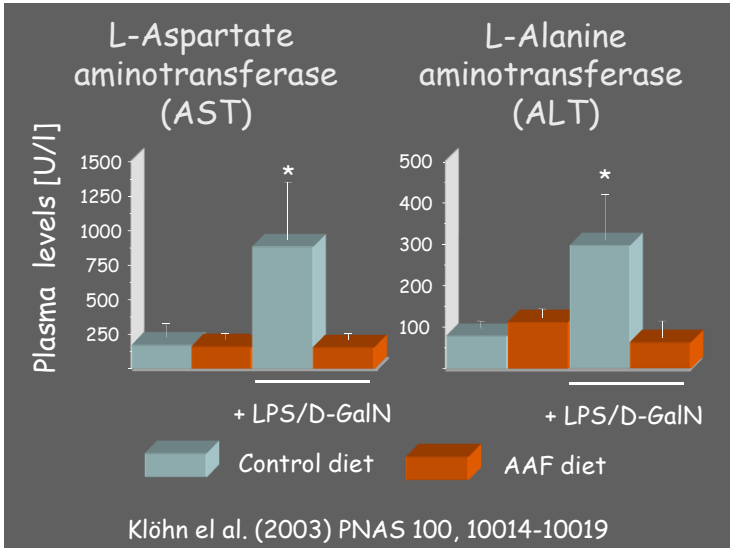


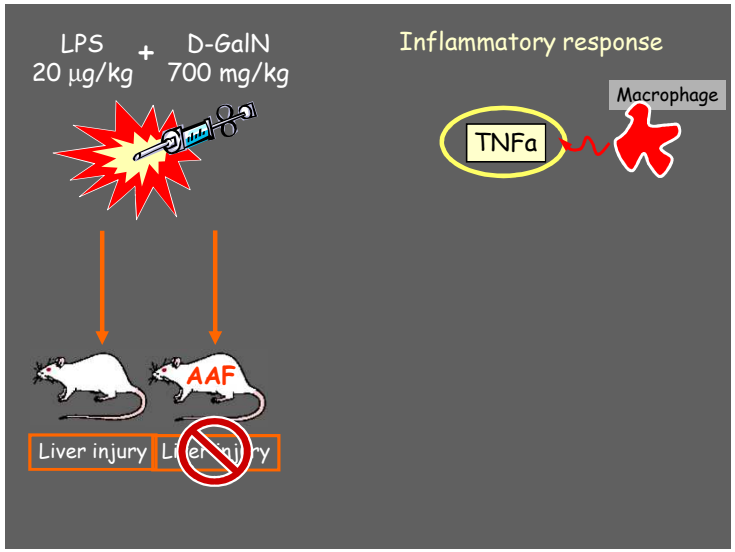
La transversione G → T è la mutazione più comune indotta da AAF


Myxothiazol
i.m.
I
II
Q
c
bc1
aa3
e-
O2
AAF
NO-F
•O-NH-F
O2
O2
SOD
HW
Fe2+
OH• + 1O2
H2O2
[after Klöhn, Brandt & Neumann]


LPS
20 µg/kg
+
D-GalN
700 mg/kg
Inflammatory response
Macrophage
TNFα
TNF R
hepatocyte
Caspase 8
BID
tBID
AAF
?
Cyt c
Caspase 3
Caspase 9


TUNEL staining
of liver cryosections
control
AAF
LPS (20 µg/kg)
+ D-GalN
Tunel-positive Hepatocytes
[cells/1000]
200
160
120
80
40
0
Control diet
AAF diet
p < 0.0001
**
+ LPS/D-GalN
Klöhn el al. (2003) PNAS 100, 10014-10019

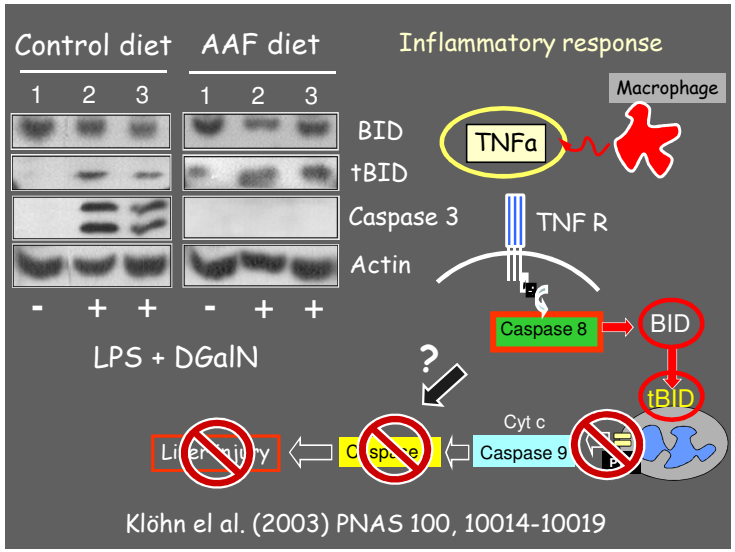

L-Aspartate
aminotransferase
(AST)
L-Alanine
aminotransferase
(ALT)
Plasma levels [U/l]
1500
1250
1000
750
500
250
500
400
300
200
100
*
*
+ LPS/D-GalN
+ LPS/D-GalN
Control diet
AAF diet
Klöhn el al. (2003) PNAS 100, 10014-10019



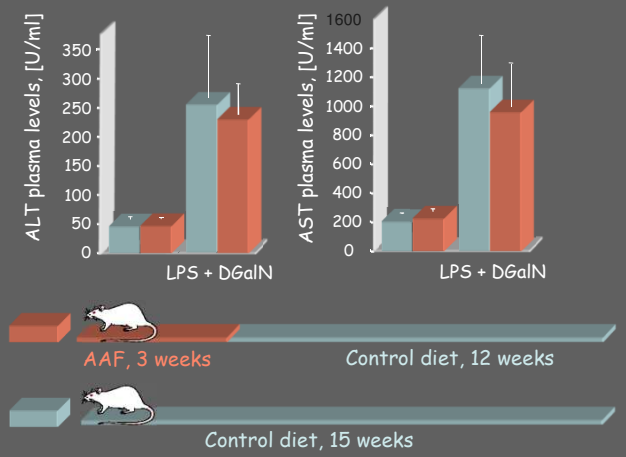
TNFα levels, fold increase at peak

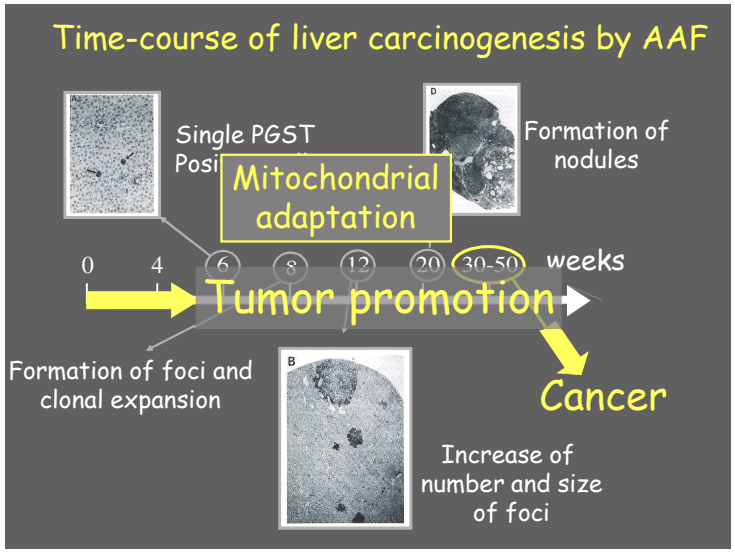
Control-fed rats …. 9.1 ± 4.8

AAF-fed rats ..... 9.1 ± 2.9



Is adaptation reversible?





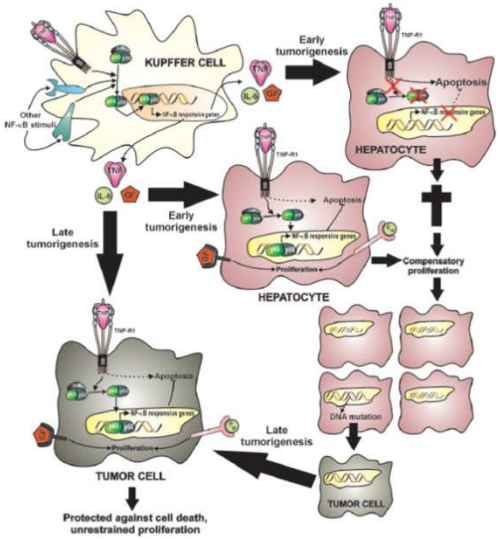
Early resistance to cell death and to onset of the mitochondrial permeability transition during hepatocarcinogenesis with 2-acetylaminofluorene

Peter-Christian Klöhn*†‡, Maria Eugenia Soriano*†, William Irwin*, Daniele Penzo*, Luca Scorrano*§, Annette Bitsch¶, Hans-Günter Neumann¶, and Paolo Bernardi*‖

*Department of Biomedical Sciences, University of Padua, Viale Giuseppe Colombo 3, I-35121 Padua, Italy; §Venetian Institute of Molecular Medicine, Via Orus 2, I-35129 Padua, Italy; and ¶Department of Toxicology, Universität Würzburg, Versbacher Strasse 9, D-97078 Würzburg, Germany

Communicated by Douglas C. Wallace, University of California College of Medicine, Irvine, CA, June 12, 2003 (received for review November 26, 2002)

10014–10019 | PNAS | August 19, 2003 | vol. 100



0163-769X/07/$20.00/0
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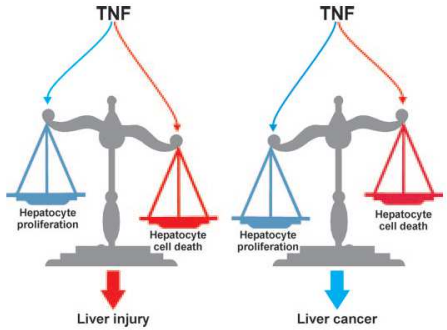
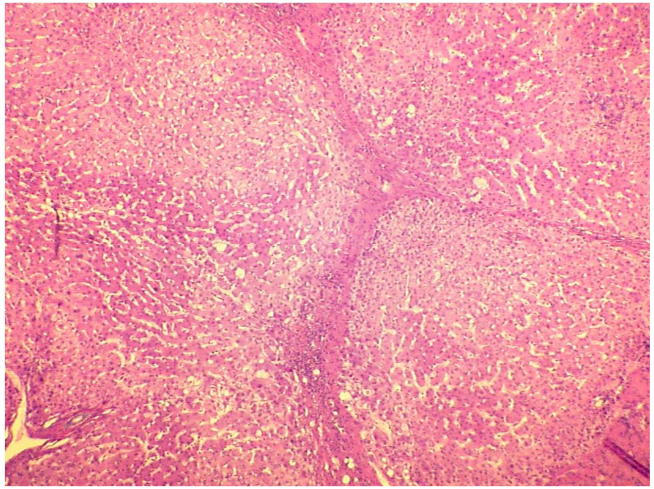
doi: 10.1210/er.2006-0031

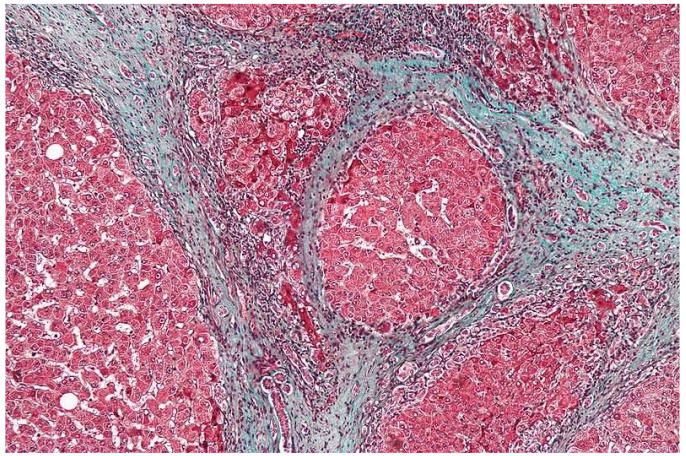
Hepatic Tumor Necrosis Factor Signaling and Nuclear Factor-κB: Effects on Liver Homeostasis and Beyond

Andy Wullaert, Geert van Loo, Karen Heyninck, and Rudi Beyaert

Unit of Molecular Signal Transduction in Inflammation, Department for Molecular Biomedical Research-VIB, and Department of Molecular Biology, Ghent University, Technologiepark 927, B-9052 Ghent (Zwijnaarde), Belgium







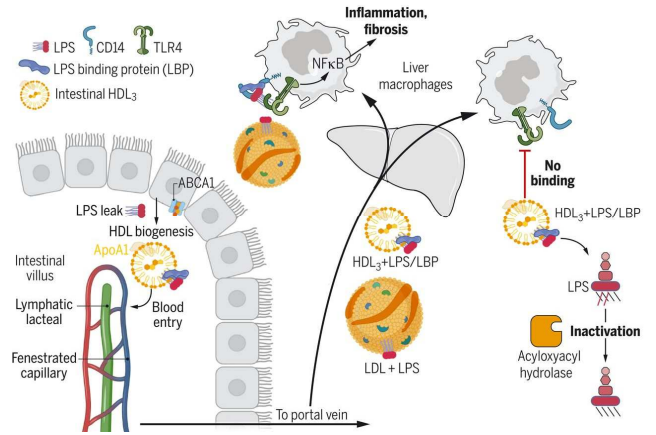
PHYSIOLOGY

Enterically derived high-density lipoprotein restrains liver injury through the portal vein

Yong-Hyun Han*, Emily J. Onufer, Li-Hao Huang, Robert W. Sprung, W. Sean Davidson, Rafael S. Czepielewski, Mary Wohltmann, Mary G. Sorci-Thomas, Brad W. Warner, Gwendalyn J. Randolph*

Han *et al.*, *Science* **373**, 410 (2021)
Han *et al.*, *Science* **373**, eabe6729 (2021)

Un nuovo ruolo per le HDL_3 enteriche



Trafficking and functional properties of enteric HDL. Enterocytes express ABCA1 to promote HDL biogenesis. The nascent HDL enters portal venous blood bearing LBP, which allows it to hide LPS from recognition by TLR4* macrophages. Failed recognition prevents macrophage activation. Although its ability to trigger macrophages is suppressed by HDL_3, LPS in the HDL_3 complex can still be inactivated by acyloxyacyl hydrolase. Figure was drawn with BioRender.

INTRODUCTION: High-density lipoprotein (HDL) participates in cholesterol homeostasis and may also have anti-inflammatory or antimicrobial roles through its interaction with numerous plasma proteins. The liver synthesizes most HDL in the body, but the intestine also produces HDL. However, a role for intestinal HDL distinct from that produced by the liver has not been identified. While remodeling its cargo, HDL particles circulate through tissue spaces, but so far, HDL trafficking within tissues has been scarcely studied.

RATIONALE: We reasoned that understanding HDL-trafficking patterns might bring insight into its roles in health and disease, including whether HDL made by the intestine is functionally redundant with that produced by the liver. Using a knock-in mouse that we previously generated to phototag HDL in any tissue location, we aimed to trace the fate of HDL synthesized by the intestine.

RESULTS: Phototagged HDL derived from small bowel enterocytes was generated most abundantly by the ileum and did not travel into draining lymphatic vessels as enterocyte-derived chylomicrons do. Instead, intestinal HDL rapidly entered the portal vein, the major blood supply to the liver. This finding raised the issue of whether the liver might benefit from intestinal HDL and pointed us to an older concept that HDL might neutralize a key microbial signal that can escape a permeable gut: lipopolysaccharide (LPS) from Gram-negative bacteria. Past studies using multiple models have shown that LPS engagement of its receptor, Toll-like receptor 4 (TLR4), in the liver drives significant liver pathology, including inflammation that progresses to fibrosis. Using biochemical, proteomic, and functional approaches, we observed that the intestine produces a particular subspecies of HDL called HDL_3. Unlike another HDL subspecies (HDL_2), HDL_3 sequestered LPS so efficiently that it could not bind to TLR4$^+$ liver macrophages. In this way, HDL_3 produced by the intestine protected the liver from the inflammation and fibrosis observed in a variety of mouse models of liver injury that parallel clinically relevant conditions in humans, including surgical resection of the small bowel, alcohol consumption, or high-fat diets. Administration of an oral drug targeting the transcription factor liver X receptor, the master regulator of genes associated with HDL biogenesis, raised enteric HDL levels and protected the mice from liver pathology. This protection was lost if mice did not express enterically derived HDL, indicating that intestinal HDL was a key target of the drug. Six samples of human portal venous blood with matched systemic venous blood confirmed the enrichment of HDL_3.

Mechanistically, LPS-binding protein (LBP) was enriched in HDL_3 particles and was required for HDL_3 to mask LPS from detection by TLR4. This finding was unexpected because LBP otherwise promotes TLR4 signaling by shuttling LPS to CD14, which then shuttles it to TLR4. Thus, HDL_3 interacts with a known component of the TLR4-signaling platform, LBP, to hide LPS from detection. Without binding to TLR4, the HDL_3-LBP-LPS complex was not retained in liver. Instead, it exited the liver while the LPS associated with it was inactivated. The enzyme acyloxyacyl hydrolase, which is produced in part by liver macrophages and which deacylates critical fatty acid residues in LPS for TLR4 activation, could still access and act upon HDL_3-associated LPS to detoxify it. Low-density lipoprotein bound LPS, but not LBP, and was thus unable to prevent LPS activation of liver macrophages. LBP is in the same family of lipid-binding proteins as phospholipid transfer protein and cholesterol ester transfer protein, which have well-established roles in remodeling the lipid configuration of HDL. Another microbial lipid, lipoteichoic acid from Gram-positive bacteria, is known to bind LBP. We found that it too complexed with HDL_3 and suppressed the activation of liver macrophages.

CONCLUSION: The production of HDL by small bowel enterocytes in a form that potently masks LPS comprises a disease tolerance strategy to protect the liver from injury of enteric origin. Enteric HDL may thus be a suitable pharmacologic target for protecting the liver against gut-derived LPS leakage in alcoholic and nonalcoholic settings. ■

Wilson's disease and other neurological copper disorders

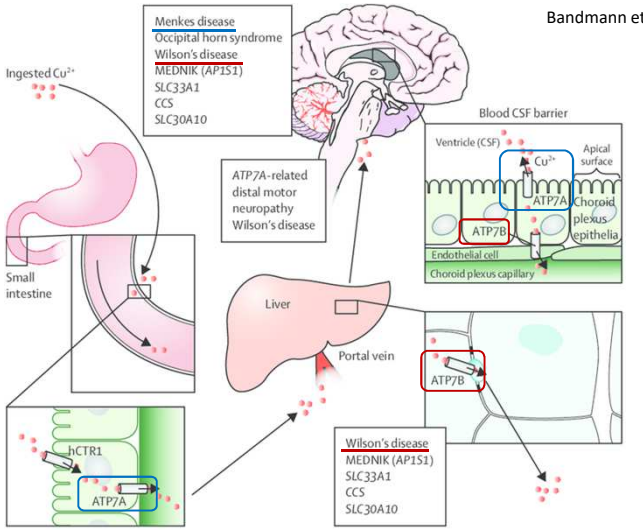
Oliver Bandmann, Karl Heinz Weiss, Stephen G Kaler

Lancet Neurol 2015; 14: 103–13

Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Sheffield, UK (Prof O Bandmann PhD); University Hospital Heidelberg, Department of Internal Medicine IV, Heidelberg, Germany (K H Weiss MD); and Section on Translational Neuroscience, Molecular Medicine Program, Eunice Kennedy Shriver National

The copper metabolism disorder Wilson's disease was first defined in 1912. Wilson's disease can present with hepatic and neurological deficits, including dystonia and parkinsonism. Early-onset presentations in infancy and late-onset manifestations in adults older than 70 years of age are now well recognised. Direct genetic testing for *ATP7B* mutations are increasingly available to confirm the clinical diagnosis of Wilson's disease, and results from biochemical and genetic prevalence studies suggest that Wilson's disease might be much more common than previously estimated. Early diagnosis of Wilson's disease is crucial to ensure that patients can be started on adequate treatment, but uncertainty remains about the best possible choice of medication. Furthermore, Wilson's disease needs to be differentiated from other conditions that also present clinically with hepatolenticular degeneration or share biochemical abnormalities with Wilson's disease, such as reduced serum ceruloplasmin concentrations. Disordered copper metabolism is also associated with other neurological conditions, including a subtype of axonal neuropathy due to *ATP7A* mutations and the late-onset neurodegenerative disorders Alzheimer's disease and Parkinson's disease.

Figure 1: **Healthy copper metabolism and the molecular mechanisms of copper disease**
Copper absorption occurs in the small intestine via enterocyte uptake by human copper transporter 1 (hCTR1) and passage into the blood mediated by ATP7A at the basolateral aspect of duodenal epithelia. Copper is conveyed to the liver via the portal circulation and excess copper is removed by excretion into the bile at the apical aspect of hepatocytes, a process impaired by mutations in *ATP7B*. Copper diseases of the liver also involve mutations in the *AP1S1* gene implicated in MEDNIK syndrome, the acetyl CoA transporter SLC33A1, and the cytosolic copper chaperone CCS. Mutations in the manganese transporter SLC30A10 produce hepatic cirrhosis due to manganese accumulation that can mimic Wilson's disease. *ATP7A* and *ATP7B* are believed to mediate copper entry and exodus, respectively, at the blood–CSF barrier of the choroid plexus epithelia. Brain copper deficiency (Menkes disease) or excess (Wilson's disease), respectively, result from mutations in these essential copper transporters. The CNS is also affected by alterations in *AP1S1*, *SLC33A1*, *CCS*, and *SLC30A10*. Isolated motor neuron degeneration occurs in association with unique *ATP7A* missense mutations affecting axonal trafficking, and sensory peripheral neuropathy can be a component of Wilson's disease. MEDNIK=mental retardation, enteropathy, deafness, neuropathy, ichthyosis, and keratodermia.



Bandmann et al.,

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Editorial

MEDNIK syndrome: a new entry in the spectrum of inborn errors of copper metabolism

Gavino Faa[1,2], Clara Gerosa[1], Massimo Castagnola[3]

www.jpnim.com Open Access eISSN: 2281-0692
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Editorial

MEDNIK syndrome: a new entry in the spectrum of inborn errors of copper metabolism

Gavino Faa[1,2], Clara Gerosa[1], Massimo Castagnola[3]

In recent years, a new autosomal recessive mucocutaneous syndrome characterized by Mental retardation, Enteropathy, Deafness, peripheral Neuropathy, Ichthyosis, and Keratodermia (MEDNIK) has been described in several French-Canadian families. Previously defined as atypical erythrokeratodermia in 1972 [9], and as erythrodermia variabilis-3 in 2005 [10], in 2008 MEDNIK syndrome has been associated with a splice mutation in the Adaptor Protein-1 S1 (*AP1S1*) gene, encoding for the small subunit σ1A of the adaptor protein (AP)-1 complex [11]. This syndrome has been subsequently described in an Italian patient [12] and a Turkish child [13].

The hypothesis that MEDNIK syndrome might represent the first example of diseases of copper metabolism associated with mutations in genes encoding for the subunits of AP complexes [14] has been recently confirmed by the report of three patients with a mutation in the *AP1B1* gene, encoding for the β1 subunit of the AP-1 complex [17]. In these patients, a MEDNIK-like syndrome was observed, with low serum copper and ceruloplasmin levels, suggesting dysfunction of copper pumps, but in the absence of liver disease due to copper overload.

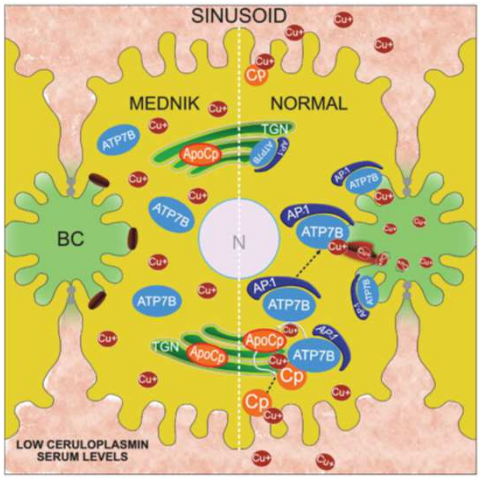
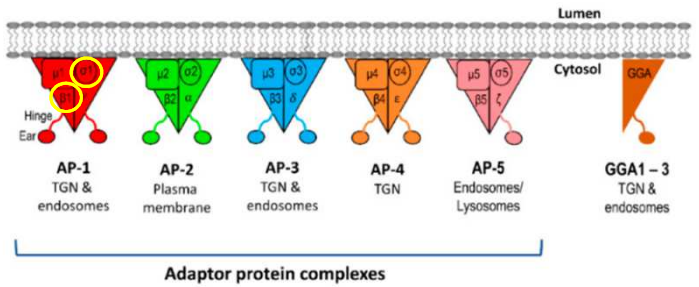


Figure 1. ATP7B trafficking inside hepatocytes.
On the right side, ATP7B in physiological conditions is mainly localized to the Trans-Golgi Network (TGN). When copper stores increase, ATP7B undergoes vesicular transport regulated by AP-1 and is transported to the biliary canaliculus (BC) membrane. In this location, ATP7B acts as a copper transporter, allowing excess copper excretion into bile. On the left side, the consequences of *AP1S1* gene mutations are summarised. The absence of AP-1 causes aberrant localisation of ATP7B, leading to copper accumulation in the hepatocyte and reduced incorporation of copper ions in apoceruloplasmin, ending with low ceruloplasmin serum levels.

Review *Cells* **2019**, *8*, 531; doi:10.3390/cells8060531

Cargo Sorting at the *trans*-Golgi Network for Shunting into Specific Transport Routes: Role of Arf Small G Proteins and Adaptor Complexes

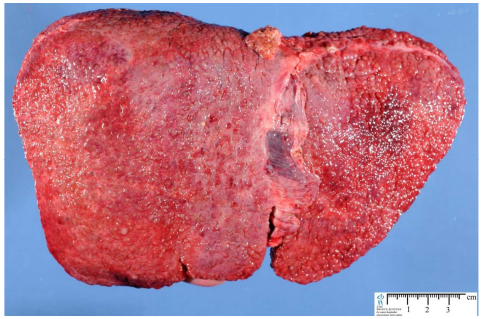
Jing Zhi Anson Tan and Paul Anthony Gleeson *



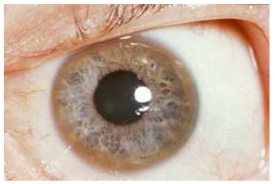
σ1 – MEDNIK
β1 – MEDNIK-like

Morbo di Wilson

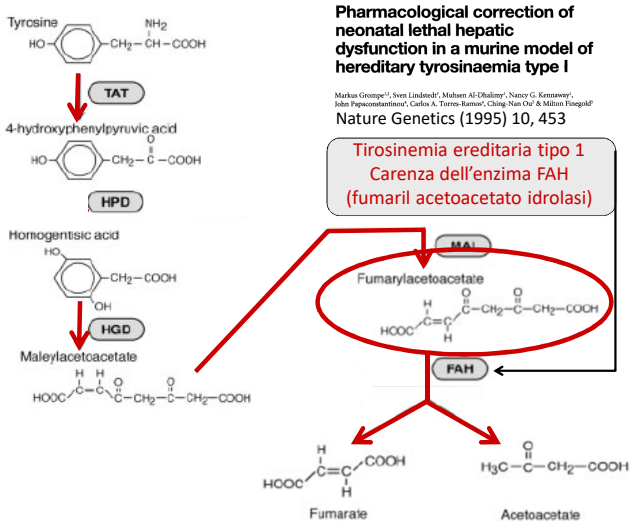
- Malattia autosomica recessiva da mutazioni nel gene (sul cromosoma 13q14.3) che codifica la proteina ATP7B, una ATPasi di tipo P che trasporta il rame e ne permette la secrezione biliare e la incorporazione nella ceruloplasmina (ferrossidasi). In assenza di ATP7B la apoproteina (apoceruloplasmina) viene secreta dal fegato e rapidamente degradata, mentre il rame si accumula soprattutto nel fegato e nel cervello innescando la reazione di Haber Weiss → danno organico .
- Oltre che per la ceruloplasmina, il rame è un elemento essenziale per la citocromo ossidasi, la dopamina β idrossilasi, una delle due forme della superossido dismutasi e la tirosinasi.
- La epatopatia evolve in cirrosi; i danni neurologici sono soprattutto a carico dei nuclei della base (putamen e globo pallido) cioè del nucleo lenticolare da cui il sinonimo della malattia «sindrome epatolenticolare», con segni che vanno dal parkinsonismo (bradikinesia con o senza tremori, atassia e/o distonia) all'emicrania, alle convulsioni e alla presenza di sintomi psichiatrici.
- Spesso è interessata la cornea, che può presentare lo patognomonico anello di Kayser-Fleischer.



Morbo di Wilson



Anello di Kayser-Fleisher

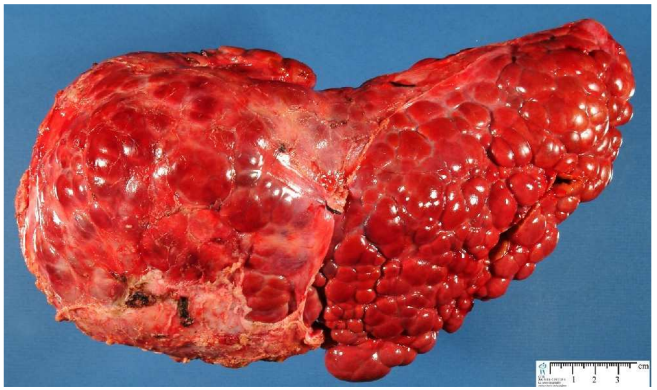


Pharmacological correction of neonatal lethal hepatic dysfunction in a murine model of hereditary tyrosinaemia type I

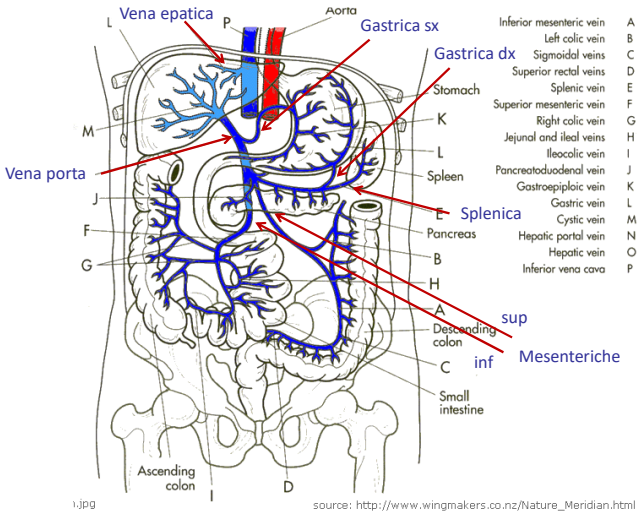
Markus Grompe[*], Sven Lindstedt[†], Muhsen Al-Dhalimy[‡], Nancy G. Kennaway[‡], John Papaconstantinou[§], Carlos A. Torres-Ramos[‖], Ching-Nan Ou[‖] & Milton Finegold[‖]

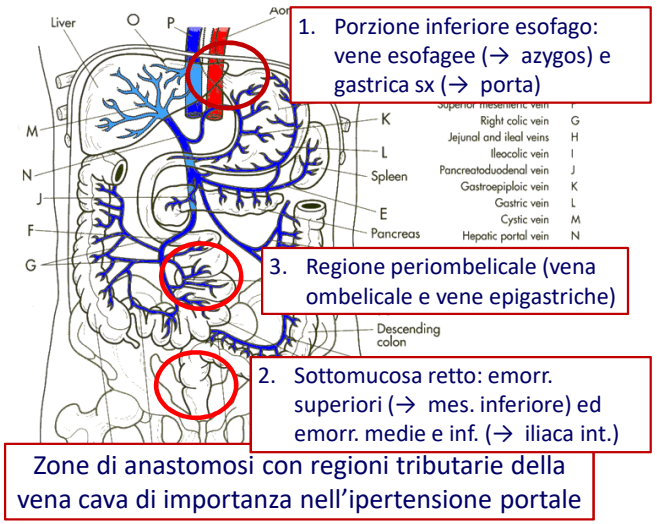
Nature Genetics (1995) 10, 453

Tirosinemia ereditaria tipo 1
Carenza dell'enzima FAH
(fumaril acetoacetato idrolasi)



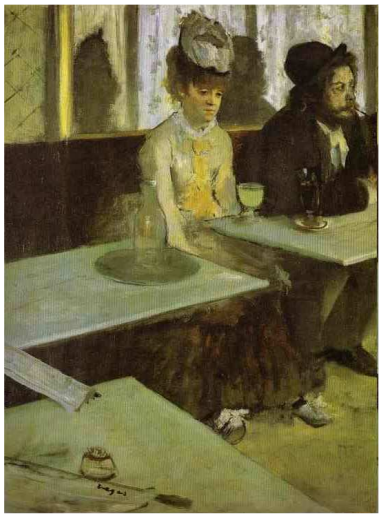
Cirrhosis and HCC focus in Tyrosinaemia, type 1





1. Porzione inferiore esofago: vene esofagee (→ azygos) e gastrica sx (→ porta)
3. Regione periombelicale (vena ombelicale e vene epigastriche)
2. Sottomucosa retto: emorr. superiori (→ mes. inferiore) ed emorr. medie e inf. (→ iliaca int.)

Zone di anastomosi con regioni tributarie della vena cava di importanza nell'ipertensione portale



Edgar Degas
L'absinthe
1876

Ipertensione portale

Aumento protratto della pressione portale causato da ostruzione venosa nel circuito portale

1. <u>Intraepatica</u>

- cirrosi epatica
- malattia cistica del fegato
- iperplasia rigenerativa nodulare
- epatocarcinoma e carcinoma metastatico
- schistosomiasi epatica (*S. mansoni, S. japonicum*)

Ipertensione portale

Aumento protratto della pressione portale causato da ostruzione venosa nel circuito portale

2. Preepatica

- trombosi della vena porta:
  tumori, infezioni, stati ipercoagulativi (contraccettivi orali), gravidanza, pancreatite, traumi chirurgici; di frequente associata a cirrosi
- grossa fistola AV

Una sindrome simile alla precedente può essere simulata da:

- insufficienza cardiaca grave
- stenosi o insufficienza tricuspidale
- pericardite costrittiva

Ipertensione portale

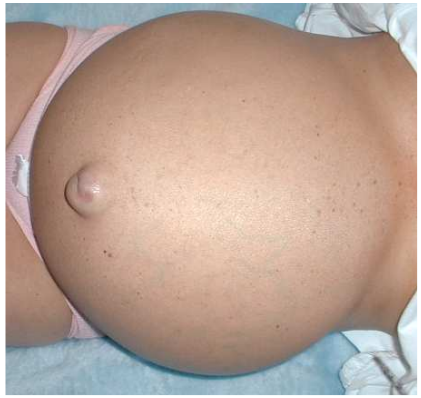
Aumento protratto della pressione portale causato da ostruzione venosa nel circuito portale

3. Postepatica

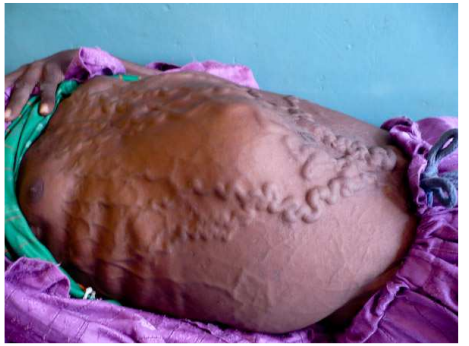
- occlusione delle vene sovraepatiche (sindrome di Budd-Chiari):
  trombosi associata a policitemia vera, tumori, epatocarcinoma, infezioni, stati ipercoagulativi;
- occlusione vene centrolobulari (antineopl., GvH)

Complicanze dell'ipertensione portale

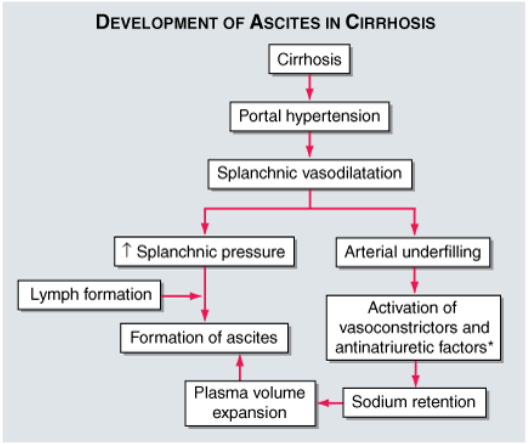
1. Varici esofagee
2. Varici anorettali
3. «Caput medusae» (non sempre)
4. Splenomegalia
5. Ascite
6. Peritonite spontanea



Ascite



«Caput medusae»



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Ittero

Colorazione giallastra della cute e delle mucose rilevabile quando la concentrazione di bilirubina nel sangue aumenta dal valore normale di 0.5 mg/100 ml a circa 1.5 mg/100 ml e oltre, anche se raramente supera i 4 mg/100 ml.

Nell'adulto, di per sé non ha grande rilevanza clinica; nel neonato, la bilirubina non coniugata può avere conseguenza catastrofiche per deposizione nei nuclei della base (kernicterus).

Bilirubina non coniugata (preepatica), insolubile in acqua, liposolubile, veicolata dall'albumina

Bilirubina coniugata (postepatica), idrosolubile

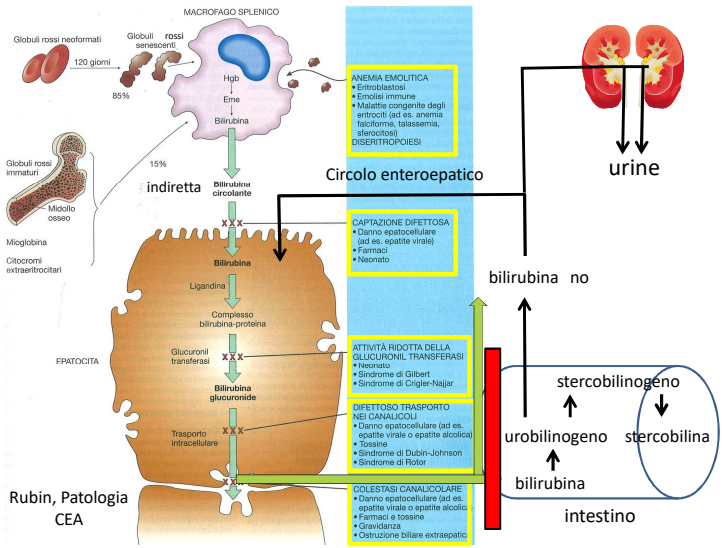
Diazoreattivo di Ehrlich

non reagisce

reagisce («diretta»)

alcool

reagisce («indiretta»)



Ridotta attività della glucuronil transferasi

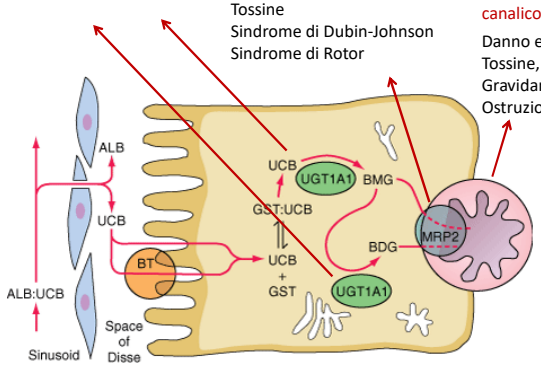
Ittero fisiologico del neonato
Sindrome di Gilbert
Sindrome di Crigler-Najjar tipo I e II

Difettoso trasporto canalicolare

Danno epatocellulare
Tossine
Sindrome di Dubin-Johnson
Sindrome di Rotor

Colestasi canalicolare

Danno epatocellulare
Tossine, farmaci
Gravidanza
Ostruzione extraepatica



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

GLI ITTERI

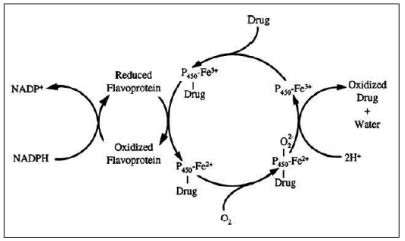
① ITTERO EMOLITICO
(a) aumento della bilirubina non coniugata plasmatica
(b) aumento dello stercobilinogeno fecale
(c) aumento dell' urobilinogeno urinario

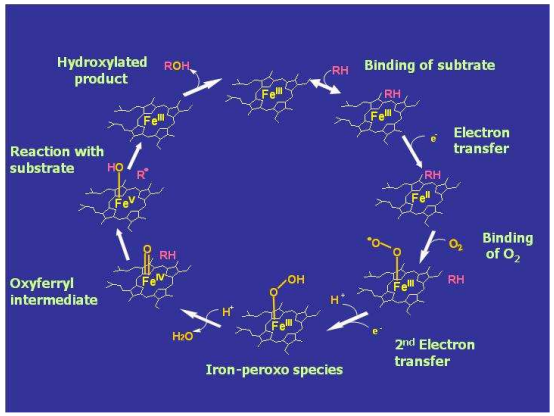
② ITTERO OSTRUTTIVO
(a) aumento della bilirubina coniugata plasmatica
(b) diminuzione dello stercobilinogeno fecale
(c) diminuzione dell' urobilinogeno urinario
(d) bilirubinuria
(e) aumento colalemia
(f) escrezione urinaria di sali biliari

③ ITTERO EPATOCELLULARE
Patogenesi complessa – in generale:
(a) aumento di bilirubina coniugata e non coniugata le altre manifestazioni, e il loro andamento, dipendono dalla noxa patogena e dal decorso della lesione epatica

Funzione detossificante

I fase: modificazione di gruppi funzionali o idrossilazione in modo da permettere la
II fase: coniugazione con composti polari → aumento solubilità





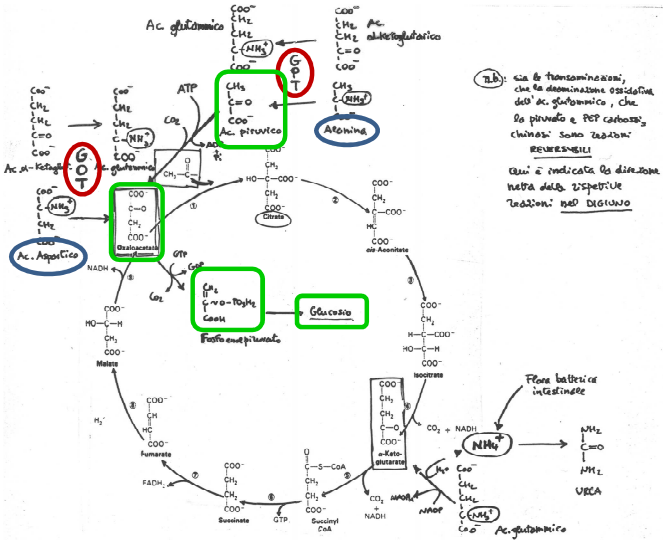
Funzione detossificante

I fase: modificazione di gruppi funzionali o idrossilazione di:

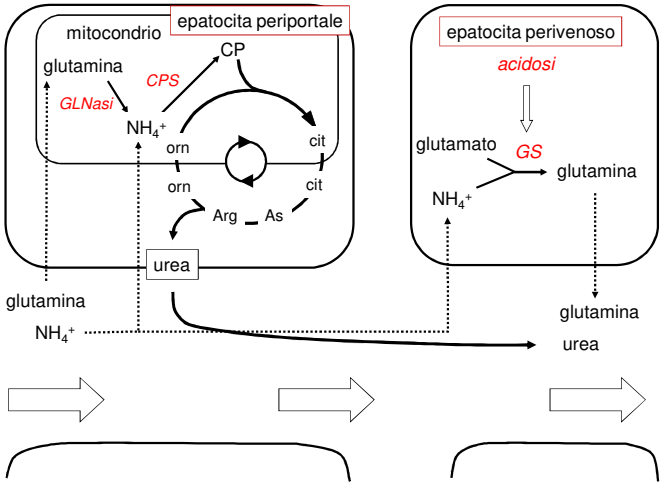
- substrati endogeni: steroidi, acidi grassi, squalene
- farmaci: barbiturici, morfina, codeina, amfetamina
- idrocarburi cancerogeni: metilcolantrene, arilamine

II fase: coniugazione con composti polari → aumento solubilità

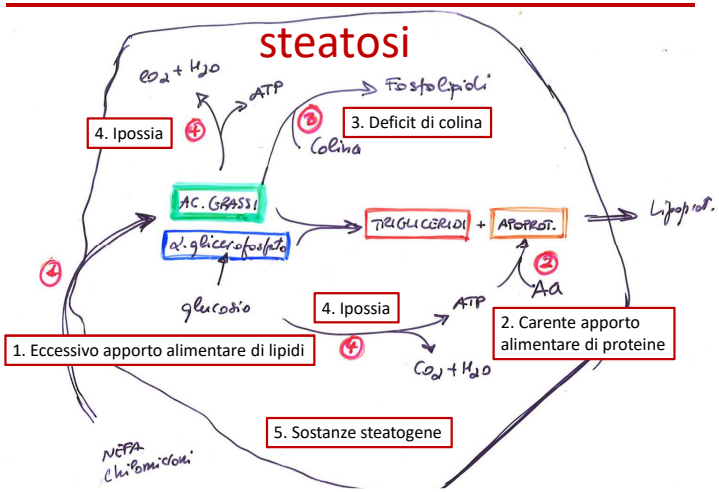
- UDP-glucuronico
- acetil-CoA
- S-adenosil-metionina
- sulfonati



Funzione metabolica: urea



Funzione metabolica: trigliceridi



5. Sostanze steatogene:

- inorganiche: fosforo giallo, asbesto, piombo

- organiche:
  - CCl_4 → perossidazione di membrana
  - Etionina → calo ATP
  - Puromicina → blocco traduzione
  - Aflatossina, amanitina → blocco trascrizione
  - Etanolo

Sintesi delle proteine plasmatiche

- Albumina
- Fattori della coagulazione
- Epcidina
- Transferrina
- Aptoglobina
- Ceruloplasmina
- α1 antitripsina
- Fattori del complemento
- ……..

Insufficienza epatica

- Disturbi del metabolismo glucidico:
  - iperglicemia (calo massa parenchima funzionante + shunt portosistemico)
  - ipoglicemia (rara)
- Disturbi del metabolismo lipidico: steatosi
- Disturbi della funzione detossificante:
  - aumento dell'emivita dei farmaci
  - rallentato metabolismo estrogeni (femminilizzazione, ginecomastia)
- Disturbi del metabolismo protidico:
  - diminuzione sintesi urea → iperammoniemia
  - diminuzione sintesi albumina → ascite, edemi
  - diminuzione sintesi fattori coagulazione, malassorbimento → tendenza alle emorragie
- Disturbi metabolismo della bilirubina: ittero

- Encefalopatia
- Complicanze endocrine
- Complicanze polmonari
- Sindrome epatorenale

James Ensor - Les mauvais médecins 1892