Il danno d'organo alcol correlato: Da Morgagni alla genetica

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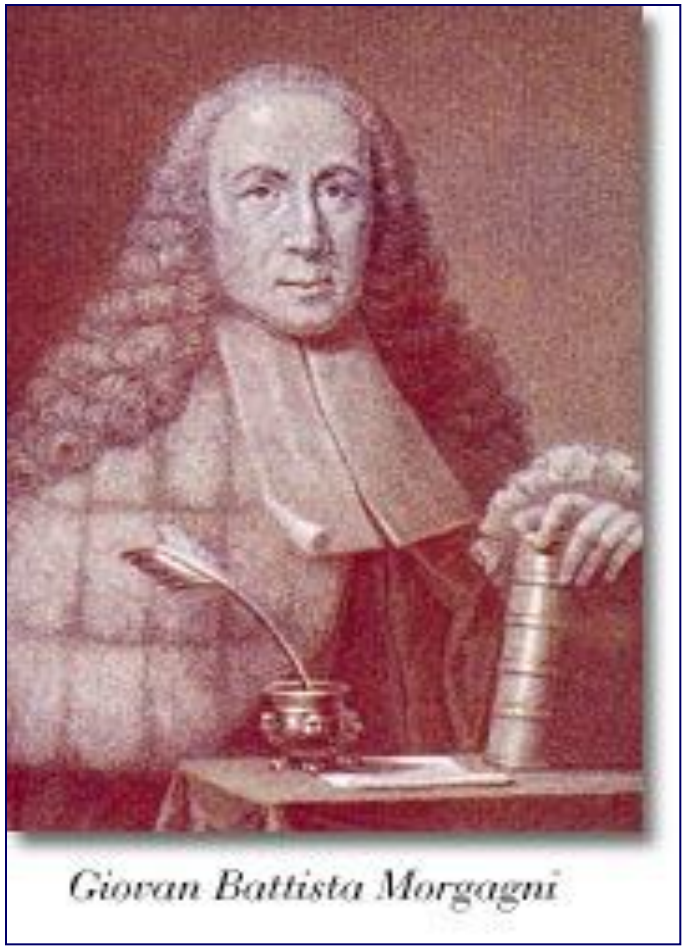
The Pathology applied to the clinical medicine

- **Giovanni Battista Morgagni (1682-1771, Forlì)**.
- He belonged to the school as a derivation Galilean, because he was a pupil of Antonio Maria Valsalva (1666-1723), who in turn was a pupil of Malpighi, Malpighi of Borelli, and he was a pupil of Galileo.
- Morgagni had a iatrofisic conception , but he was not using the microscope, used the eye: he had a tendency to try to discover the human body as a machine.



Giovan Battista Morgagni

Giovanni Battista Morgagni

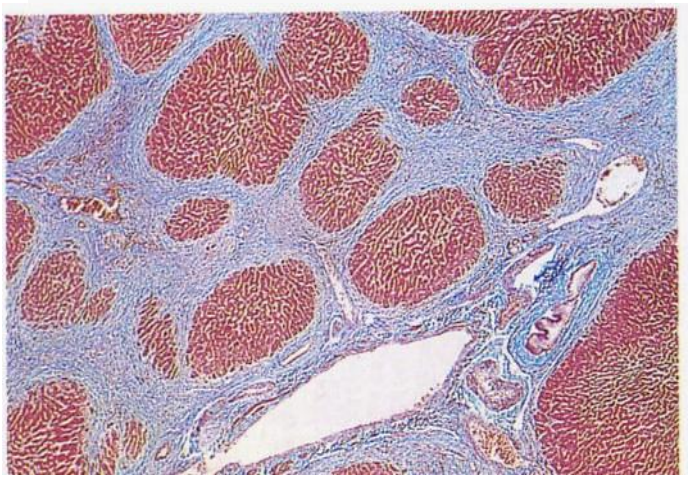
- Doctor, poet, archaeologist, classicist
- Chair of Anatomy at the University of Padua in 1629, remaining for fifty-six years
- Unitary vision of the anatomy and pathology of the one part and the other part of the clinical data
- Link between autopsy and clinical data
- Founder of modern pathological anatomy

Giovanni Battista Morgagni

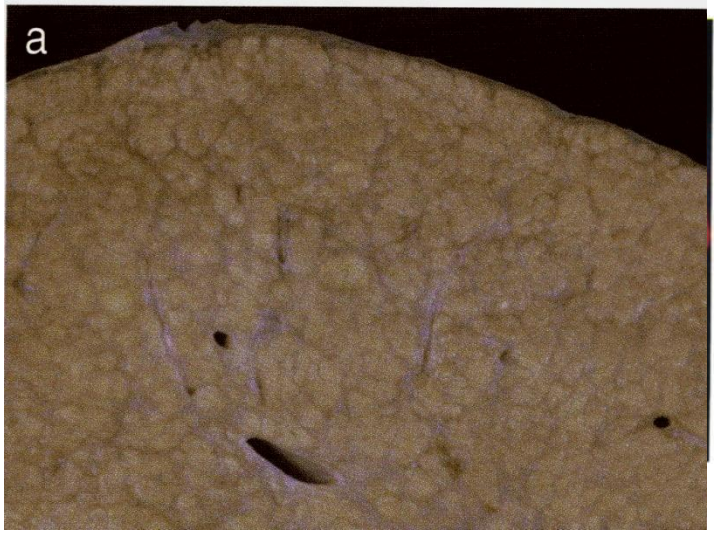
- Clinical history and necropsy description of at least 700 cases
- Original findings: liver cirrhosis, hepatisation lung in pneumonia, many tumors
- First to demonstrate that the brain abscess is a consequence and not the cause of purulent otitis

HEPATIC CIRRHOSIS
Morphological alterations

- Diffuse process
- Fibrosis
- Nodules
- Alteration of the normal architecture
- Rigeneration



- Micronodular (<3mm)
- Macronodular (>3mm)
- Mixed micro/macronodular
- septal incomplete
- “Cardiac Cirrhosis”



Pubblicazioni scientifiche

- Ethanol induces secretion of oxidized proteins by pancreatic acinar cells.Palmieri VO, Grattagliano I, Palasciano G.Cell Biol Toxicol. 2007 Nov;23(6):459-64. Epub 2007 Apr 12.
- Chronic ethanol administration induces oxidative alterations and functional impairment of pancreatic mitochondria in the rat.Grattagliano I, Palmieri V, Vendemiale G, Portincasa P, Altomare E, Palasciano G.Digestion. 1999 Nov-Dec;60(6):549-53.
- Acute ethanol administration induces oxidative changes in rat pancreatic tissue.Altomare E, Grattagliano I, Vendemiale G, Palmieri V, Palasciano G.Gut. 1996 May;38(5):742-6.
- Prolonged consumption of moderate doses of alcohol and in vitro gastro-duodenal and ileal contractility in the rat.Palasciano G, Portincasa P, Di Ciaula A, Palmieri V.Eur J Clin Invest. 1995 Mar;25(3):171-5.
- Hepatotoxicity of polyunsaturated fatty acids in alcohol abuser.Grattagliano I, Palmieri VO, Palasciano G.J Hepatol. 2002 Aug;37(2):291-2. No abstract available.
- Mitochondrial oxidative damage and myocardial fibrosis in rats chronically intoxicated with moderate doses of ethanol.Vendemiale G, Grattagliano I, Altomare E, Serviddio G, Portincasa P, Prigigallo F, Palasciano G.Toxicol Lett. 2001 Sep 15;123(2-3):209-16.

Pubblicazioni scientifiche “storiche” su Pancreas ed Alcol

- Effects of intravenous alcohol on pancreatic and biliary secretion in man.Planche NE, **Palasciano G, Meullenet J, Laugier R, Sarles H.Dig Dis Sci. 1982 May;27(5):449-53**
- Chronic alcoholism and canine exocrine pancreas secretion. A long term follow-up study.Sarles H, Tiscornia O, **Palasciano G.Gastroenterology. 1977 Feb;72(2):238-43.**
- The effects of acute and chronic **ethanol administration on canine bile secretion.Dzieniszewski J, Tiscornia OM, Palasciano G, Domingo N, Cavarz N A, Teixeira AS, Sarles H.Am J Dig Dis. 1976 Dec;21(12):1037-43.**
- Simultaneous changes in pancreatic and gastric secretion induced by acute intravenous **ethanol infusion. Effect of atropine and reserpine.Tiscornia OM, Palasciano G, Dzieniszewski J.Am J Gastroenterol. 1975 May;63(5):389-95.**
- Action of intragastric **ethanol on the pancreatic secretion of conscious rats.Cavarzan A, Teixeira AS, Sarles H, Palasciano G, Tiscornia O.Digestion. 1975;13(3):145-52.**
- Chronic alcoholism and endogenous gastrin.Treffot MJ, Tiscornia OM, **Palasciano G, Hage G, Sarles H.Am J Gastroenterol. 1975 Jan;63(1):29-32.**
- **Atropine and exocrine pancreatic secretion in alcohol-fed dogs.Tiscornia OM, Palasciano G, Sarles H.Am J Gastroenterol. 1975 Jan;63(1):33-6.**
- **Pancreatic changes induced by chronic (two years) ethanol treatment in the dog.Tiscornia OM, Palasciano G, Sarles H.Gut. 1974 Oct;15(10):839. No abstract available.**
- The effects of pentolinium and vagotomy on the inhibition of canine exocrine pancreatic secretion by intravenous **ethanol.Tiscornia OM, Hage G, Palasciano G, Brasca AP, Devaux MA, Sarles H.Biomedicine. 1973 Mar;18(2):159-63. No abstract available.**

Il danno d'organo alcol correlato

- Sistema nervoso centrale (Wernicke's syndrome; Korsakoff's syndrome; degenerazione cerebellare; disturbi del comportamento e psichiatrici)
- Sistema nervoso periferico (neuropatia)
- Apparato gastrointestinale (esofago, stomaco, pancreas, fegato)
- Tumori
- Sistema emopoietico
- Sistema cardiovascolare
- Sistema genito-urinario, funzione sessuale
- Sviluppo fetale
- Apparato muscolare e scheletrico
- Modificazioni ormonali (surrene, tiroide)

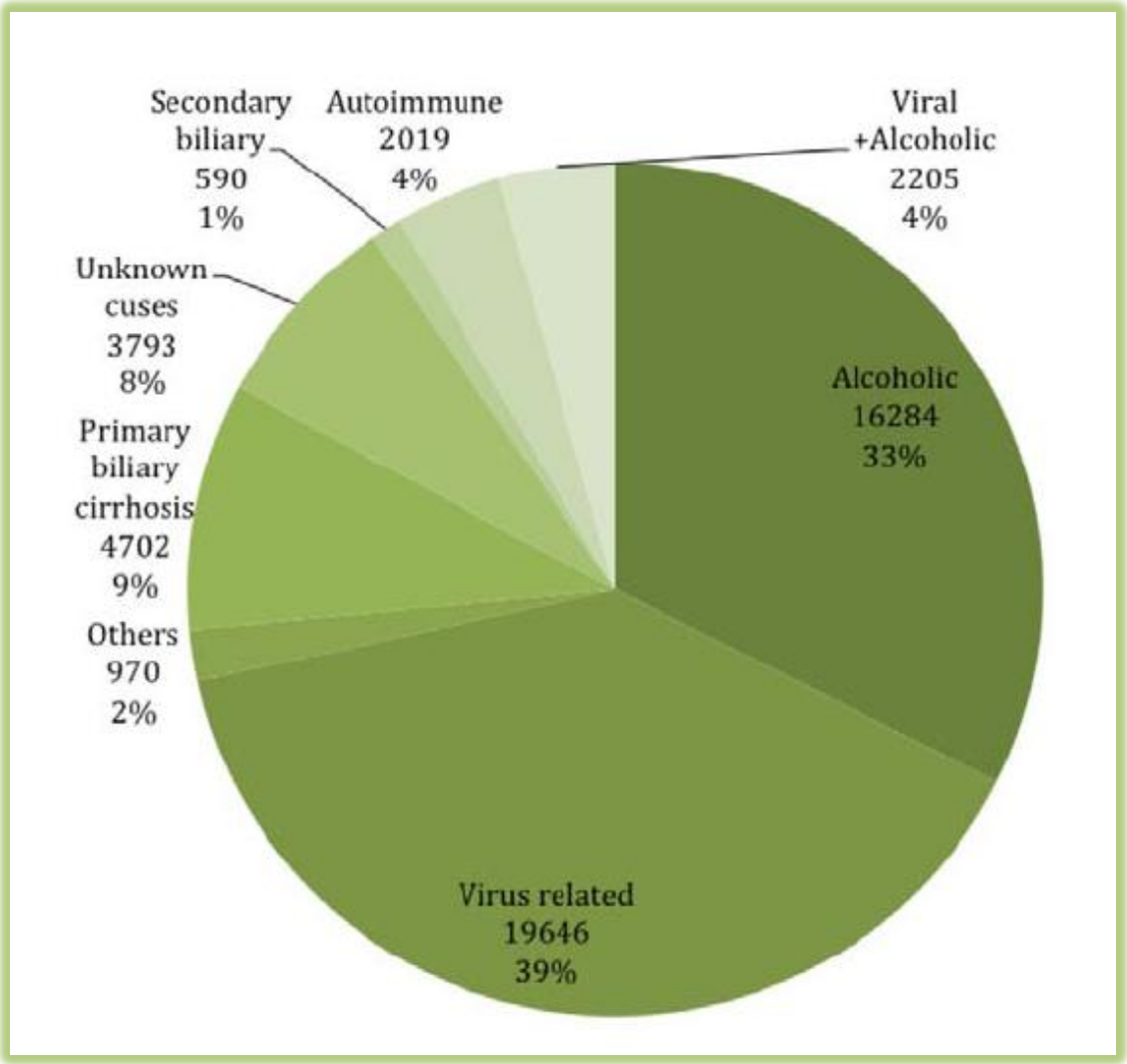
European Journal of Clinical Investigation (1995) **25,** 171–175

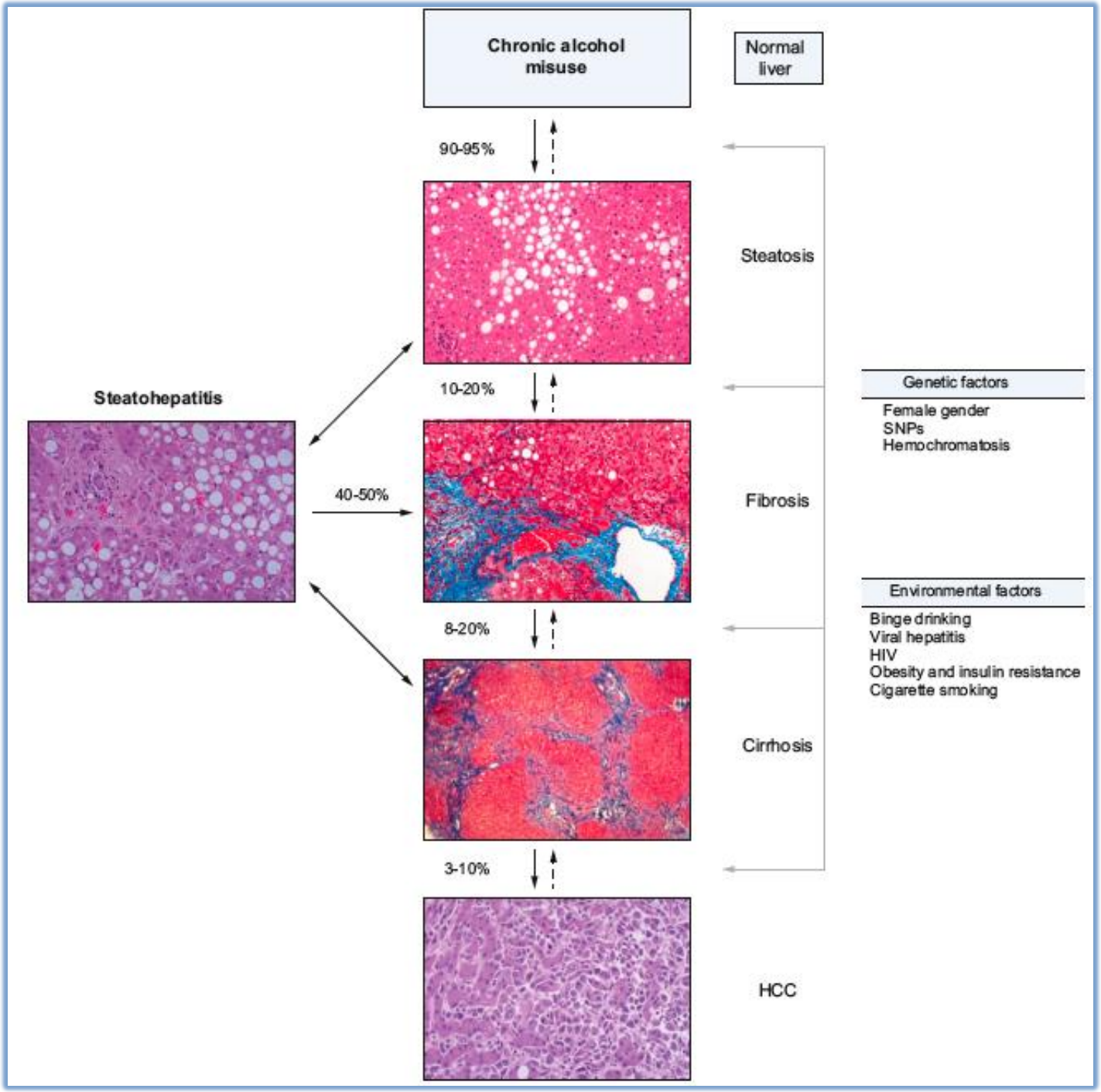
Prolonged consumption of moderate doses of alcohol and *in vitro* gastro-duodenal and ileal contractility in the rat

G. PALASCIANO, P. PORTINCASA, A. DI CIAULA & V. PALMIERI Institute of Clinica Medica I, University of Bari Medical School, Policlinico, Bari, Italy

Abstract. The effects of chronic feeding with moderate doses of ethanol (3% vol/vol in drinking water for 8 weeks), which do not induce tolerance, dependence and withdrawal, on the contractility of gastric, duodenal and ileal strips from rats were investigated. Only mens. It is concluded that, in the rat, moderate doses of ethanol given chronically impair both spontaneous and tonic contractility of the stomach and duodenal muscle without affecting ileal contraction. It is possible that motility defects in the gut exposed to ethanol concentrations which do not cause tolerance, dependence or withdrawal in the rat may be due to a local rather than a systemic effect on the smooth muscle.

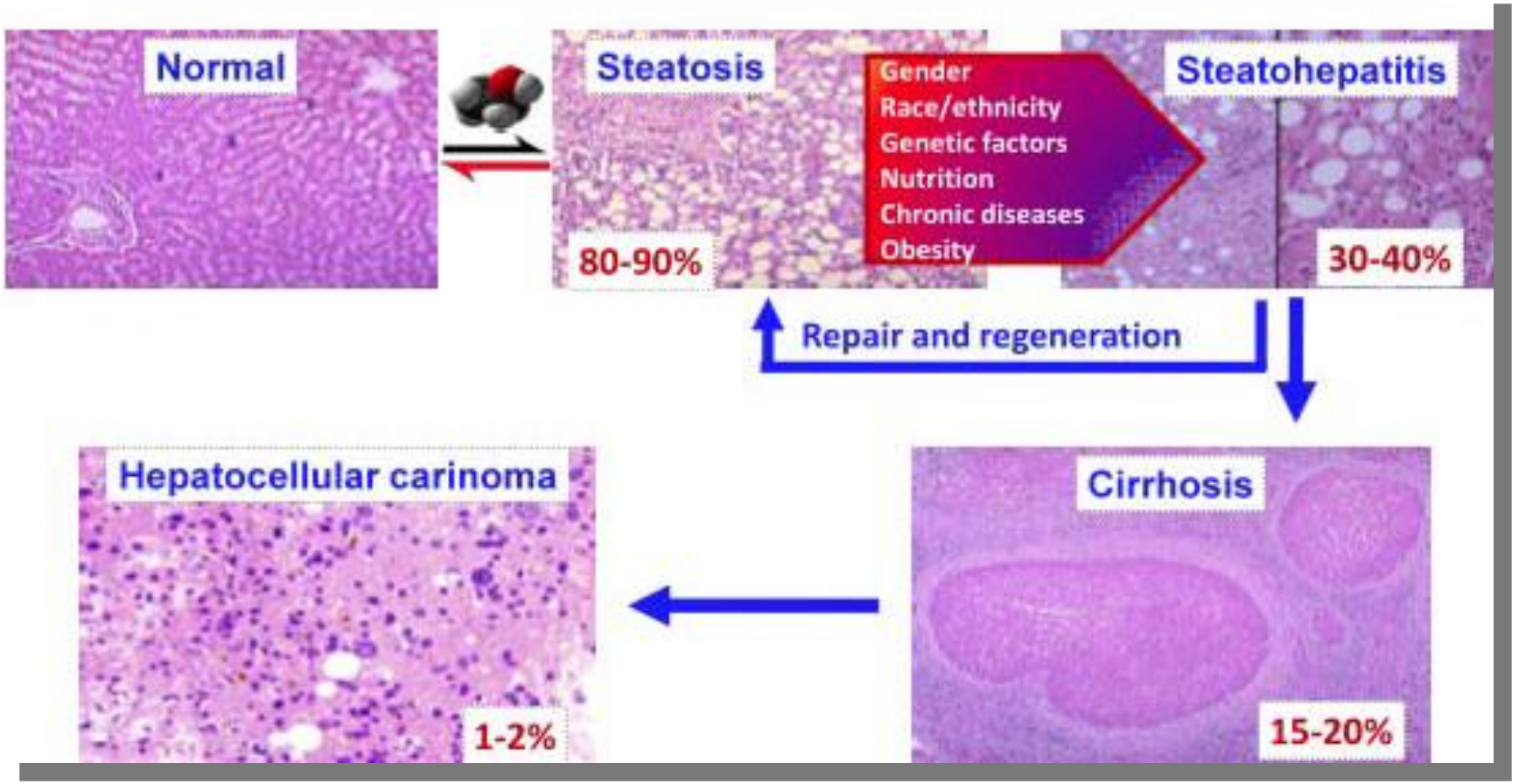
Liver transplantion in Europe. Indications in cirrhosis. Data from European Liver Transplantation Registry (ELTR) 2010





Natural history of alcoholic liver disease (ALD). The spectrum of ALD is comprised of steatosis, steatohepatitis, fibrosis, cirrhosis, and superimposed hepatocellular carcinoma.

Spectrum of Alcohol-Induced Hepatic Pathology



AASLD PRACTICE GUIDELINES

HEPATOLOGY, 2010

Alcoholic Liver Disease

Robert S. O'Shea, Srinivasan Dasarathy, Arthur J. McCullough, and the Practice Guideline Committee of the American Association for the Study of Liver Diseases and the Practice Parameters Committee of the American College of Gastroenterology

Clinical Practical Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practical Guidelines: Management of Alcoholic Liver Disease

European Association for the Study of the Liver*,†

J HEPATOLOGY, 2012

Pathogenesis of ALD

- Although many individuals consuming more than 60 g of alcohol per day develop steatosis, only a minority of the patients with steatosis progress to ASH and 10–20% eventually develop cirrhosis
- Genetic and nongenetic factors modify both the individual susceptibility and the clinical course of ALD
- The mechanisms of ALD are not completely understood and the pathogenesis varies in different stages of the disease

Alcoholic fatty liver: pathogenetic factors

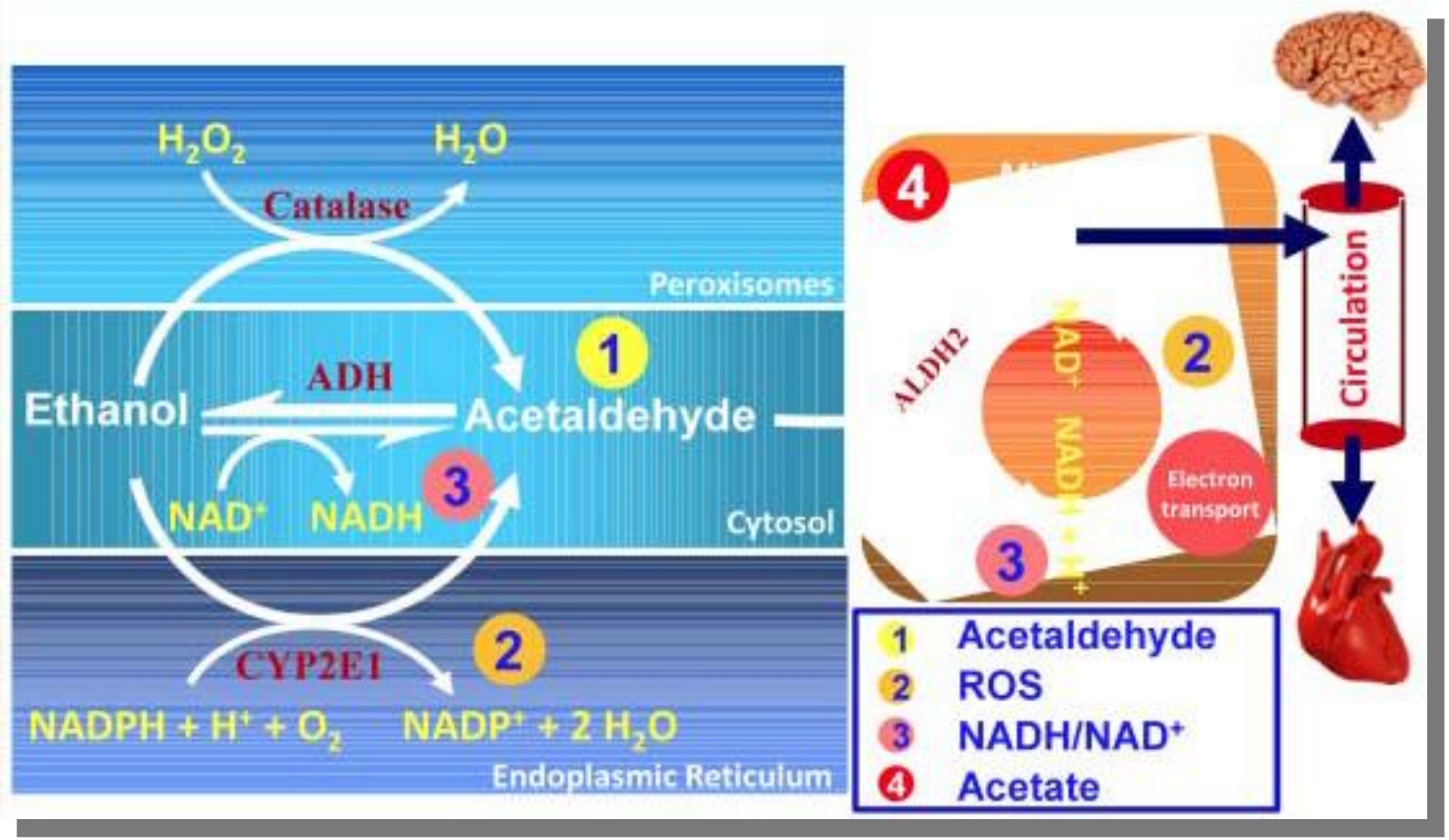
(1) Increased generation of NADH caused by alcohol oxidation, favouring fatty acid and triglyceride synthesis, and inhibiting mitochondrial b-oxidation of fatty acids.

(2) Enhanced hepatic influx of free fatty acids from adipose tissue and of chylomicrons from the intestinal mucosa.

(3) Ethanol-mediated inhibition of adenosine monophosphate activated kinase (AMPK) activity resulting in increased lipogenesis and decreased lipolysis by inhibiting peroxisome proliferating-activated receptor a (PPARa) and stimulating sterol regulatory element binding protein 1c (SREBP1c).

(4) Damage to mitochondria and microtubules by acetaldehyde, results in a reduction of NADH oxidation and the accumulation of VLDL, respectively.

Oxidative Pathways of Alcohol Metabolism



ALD: CONSEQUENCES OF INCREASED NADH/NAD+ RATIO:

- Alcoholic hypoglycemia
- Alcoholic acidosis
- Hyperuricemia
- Hypertriglyceridemia
- Hypoxia

Alcoholic steatohepatitis - 1

- Alcoholic fatty livers can develop parenchymal inflammation (mainly by PMN cells) and hepatocellular damage, a prerequisite for progress to fibrosis and cirrhosis

- Various factors may contribute to the development of ASH:
  - Acetaldehyde-induced toxic effects (protein, DNA, mitochondria, glutathione)
  - Impaired ubiquitin–proteasome pathway leading to hepatocellular injury and hepatic inclusions of aggregated cytokeratins (i.e. Mallory–Denk bodies)
  - Reactive oxygen species (ROS) generation and the resulting lipid peroxidation with DNA adduct formation
  - Pro-inflammatory cytokines

Alcoholic steatohepatitis – 2
ROS generation and DNA adduct formation

- Main sources of ROS include CYP2E1-dependent MEOS, mitochondrial electron transport system of the respiratory chain, NADH-dependent cytochrome reductase, and xanthine oxidase

- Moreover, chronic alcohol intake markedly up-regulates CYP2E1, which metabolizes ethanol to acetaldehyde and parallels the generation of ROS and hydroxyl–ethyl radicals.

Alcoholic steatohepatitis – 3
Pro-inflammatory cytokines

- Alcohol metabolites and ROS stimulate signaling pathways such as NFjB, STAT-JAK, and JNK in hepatic resident cells, leading to the local synthesis of inflammatory mediators such as TNFa and CXC chemokines (e.g. interleukin- 8), as well as osteopontin.

- Alcohol consume also results in changes in the colonic microbiota and increased intestinal permeability, leading to elevated serum levels of lipopolysaccharides that induce inflammatory actions in Kupffer cells via CD14/TLR4.

- The resulting inflammatory milieu in the alcoholic liver leads to PMN infiltration, ROS formation and hepatocellular damage

Fibrosis progression

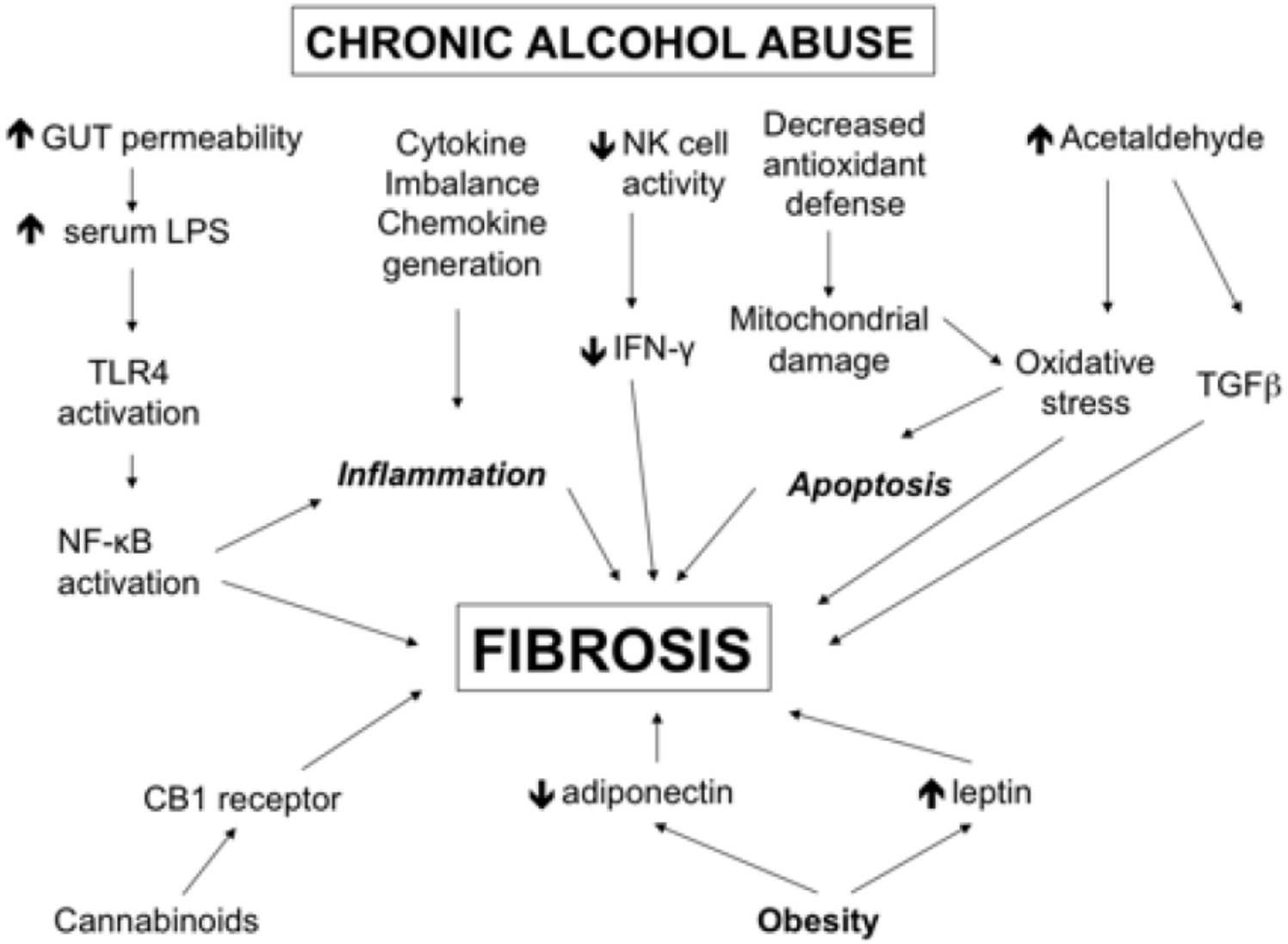
- Alcohol metabolites such as acetaldehyde can directly activate hepatic stellate cells (HSC), the main collagen producing cells in the injured liver. HSC can also be activated paracrinally by damaged hepatocytes, activated Kupffer cells and infiltrating PMN cells.

- These cells release fibrogenic mediators such as growth factors (TGFb1, PDGF), cytokines (leptin, angiotensin II, interleukin-8, and TNFa), soluble mediators (nitric oxide), and ROS.

- ROS stimulate pro-fibrogenic intracellular signaling pathways in HSC including ERK, PI3K/AKT, and JNK, up-regulate TIMP-1 and decrease the actions of metalloproteinases, thereby promoting collagen accumulation.

- Cells other than HSC can also synthesize collagen in ALD. They include portal fibroblasts and bone-marrow derived cells.

Fibrosis progression in ALD

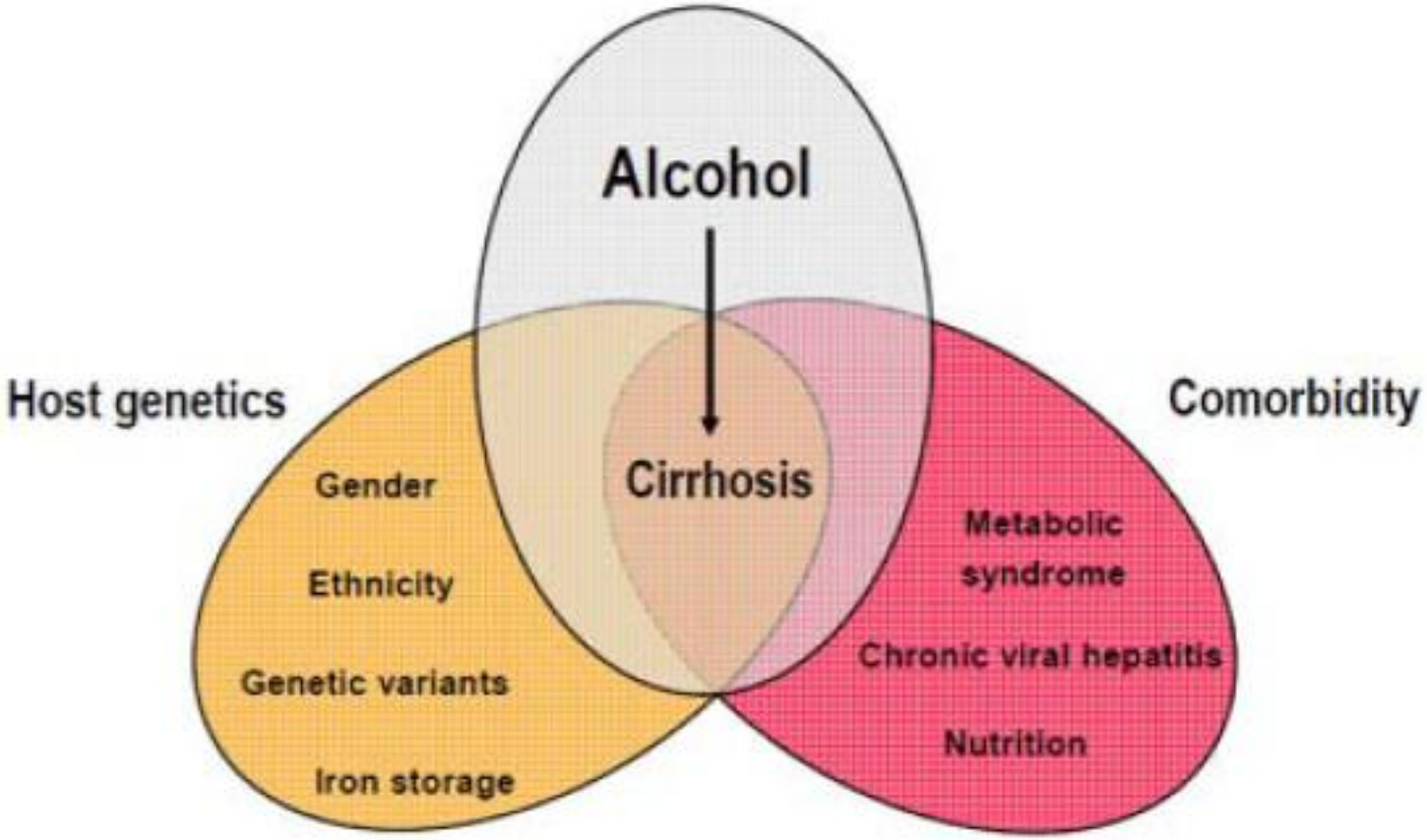


Risk factors for disease progression in alcoholic liver disease

- Non-genetic or environmental factors:
  - amount and type of alcoholic beverage,
  - the duration of consume
  - patterns of drinking.

- Genetic or host factors:
  - Gender, ethnicity,
  - coexisting conditions such as metabolic syndrome, iron overload, and infection with chronic hepatitis viruses
  - Host genetc factors

Factors of progression in ALD



Diet related risk factor for fibrosis progression

- Obesity and metabolic syndrome
- Several studies show that obesity is the single most important risk factor determining the risk of cirrhosis in heavy drinkers.
- The synergy between obesity and heavy alcohol intake presumably reflects similar mechanisms of disease for both ALD and non-alcoholic fatty liver disease, along with the direct fibrogenic effects of expanded larger mass of adipose tissue (via high levels of noradrenaline, angiotensin II and leptin, and low levels of adiponectin).

Genetic susceptibility to ALD

- Comparison of the allelic and/or genotypic frequencies of certain genetic variants (i.e. single nucleotide polymorphisms; SNP) between alcoholic cirrhosis and alcoholics without liver disease or healthy controls

- While there were significant associations between certain genetic variants and the risk of alcoholism, no overall association of any of the tested SNPs with alcoholic cirrhosis was detected.

- Recently, two candidate gene case control studies in alcoholics found a significant association between the risk of alcoholic cirrhosis and carriage of genotype PNPLA3 rs738409 (GG) in Mestizo subjects and Caucasians.

Study	Design	Patients	Results
Tian et *al.* *	Genetic case control 482 cases (alcoholic cirrhosis) (Mestizo subjects with strong ethnic heterogeneity)	482 cases (alcoholic cirrhosis) 434 non-cirrhotic ALD 305 alcoholics w/o liver enzyme elevations	rs738409 GG associated with cirrhosis when compared to controls (OR 2.25, 1.74-2.9; 1.7×10^{-10}) and to non-cirrhotic ALD (OR 1.43, 1.15-1.78, 1.0×10^{-3}) Association robust after ancestry correction (OR 1.81, 1.36-2.41; 4.7×10^{-5})
Seth et *al.* *	Genetic case control (British Caucasians)	266 cases (alcoholic cirrhosis) 182 controls (heavy drinkers w/o clinical ALD)	rs738409 G homozygosity associated with alcoholic cirrhosis (OR 7.34, 2.19-24.52, p=0.0012) Carriage of rs738409 G allele associated with alcoholic cirrhosis (OR 1.95, 1.34-2.84, p=0.00002)
Trépo et *al.* *	Genetic case control (Belgium Caucasians)	330 cases (97% biopsy-proven ALD; 263 cirrhotics) 328 controls (healthy individuals without ALD)	rs738409 G associated with ALD (OR 1.54; 1.12-2.11, p=0.008) and alcoholic cirrhosis (OR 2.08; 1.15-3.77, p=0.02) PNPLA mRNA expression inversely correlated with cirrhosis and portal pressure
Stickel et *al.* *	Genetic case control (German Caucasians)	Multicenter sample with 1,043 alcoholics (210 cirrhosis, 394 non-cirrhotic ALD, 439 alcoholic controls Population-based sample with 376 alcoholics (269 non-cirrhotic ALD, 107 alcoholic controls) Non-alcoholic healthy subjects (n=162)	Genotype rs738409 GG associated with alcoholic cirrhosis (OR 2.79, 1.55-5.04, $p=1.18 \times 10^{-5}$, cirrhosis vs. controls) Genotype rs738409 GG associated with alanine aminotransferase elevation (OR 2.33, 1.27-4.26, p=0.0085) Confirmation of association in separate replication sample (OR 4.75, 1.08-20.9, p=0.04, ALD vs alcoholic controls) Population-attributable risk of rs738409 to cirrhosis 26.6%

Risk factors for ALD and fibrosis progression

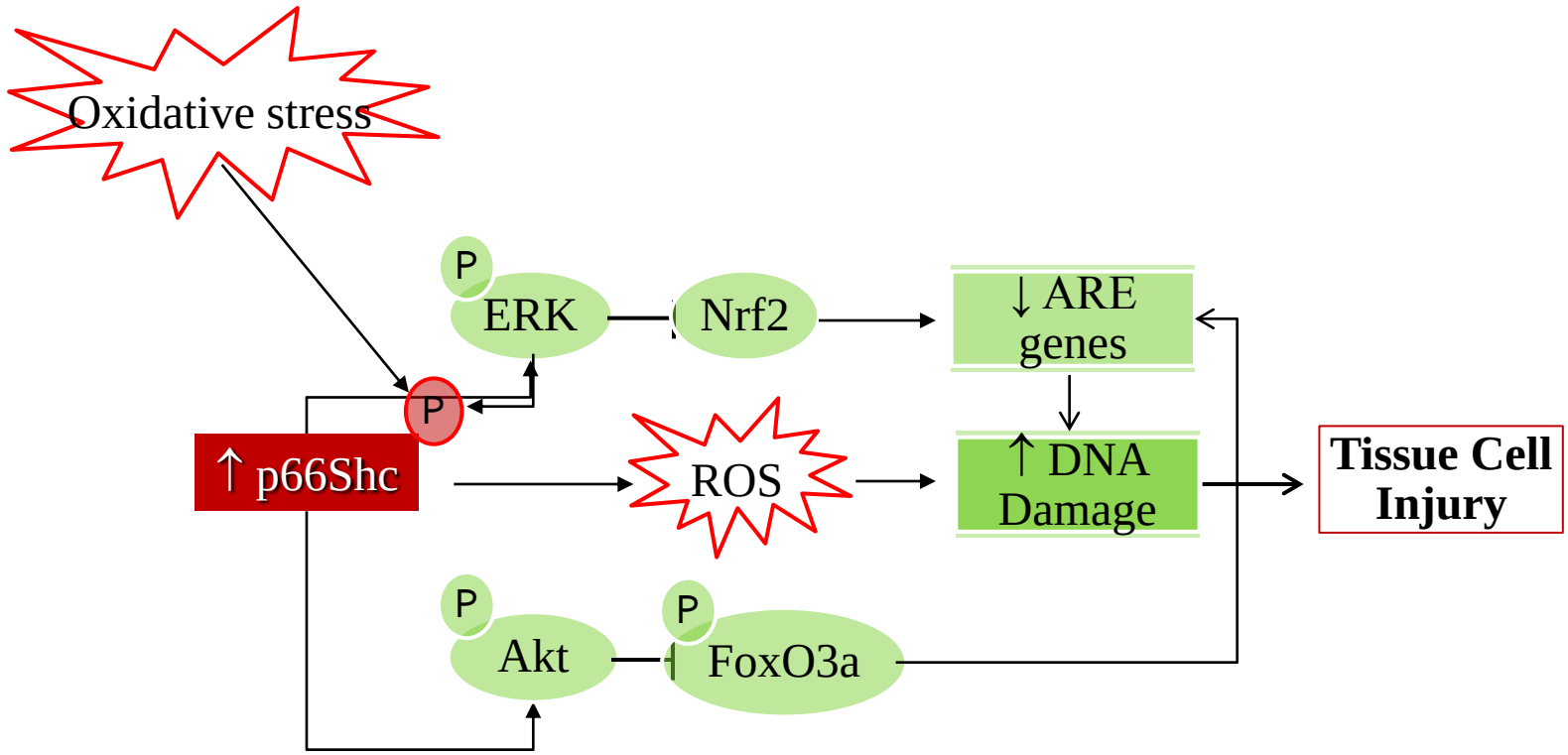
(1) Large genome-wide association studies should identify the genetic determinants implicated in individual susceptibility to develop ALD.

   (1) E.g.:Whether *PNPLA3 genotype represents a marker that will assist decision-making in clinical practice remains to be shown, as well as whether it could serve as a therapeutic target.*

(2) The interaction between environmental and genetic factors should be investigated.

(3) Additional studies are required to identify the factors influencing disease regression after drinking cessation and long-term outcome in abstinent patients

ALD pathogenesis: from Morgagni To genes and DNA damage



Perrini, Palmieri, Giorgino, Palasciano, 2013, submitted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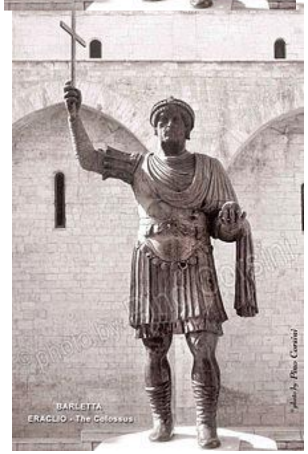
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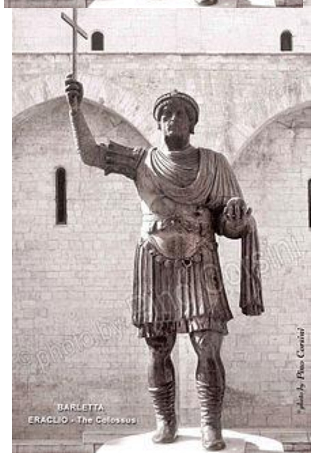
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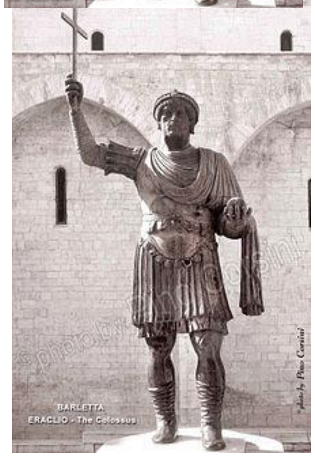
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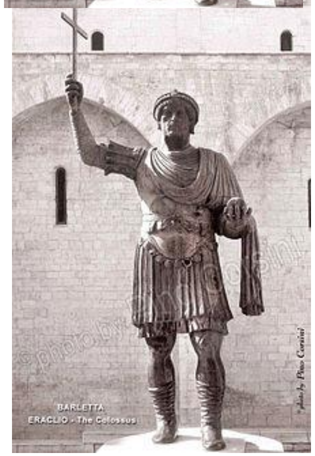
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