2017

Progetto Ematologia Romagna

Un incontro casuale con una iperferritinemia: inquadramento

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Dichiarazione di interessi con industrie farmaceutiche

- Advisory Board: Vifor, Novartis, La Jolla Pharmaceuticals

Outline

- Introduzione: la ferritina e le iperferritinemia
- Cause e meccanismi
- Patogenesi e fisiopatologia di forme paradigmatiche
- L'approccio clinico

Introduzione

Il dato laboratoristico

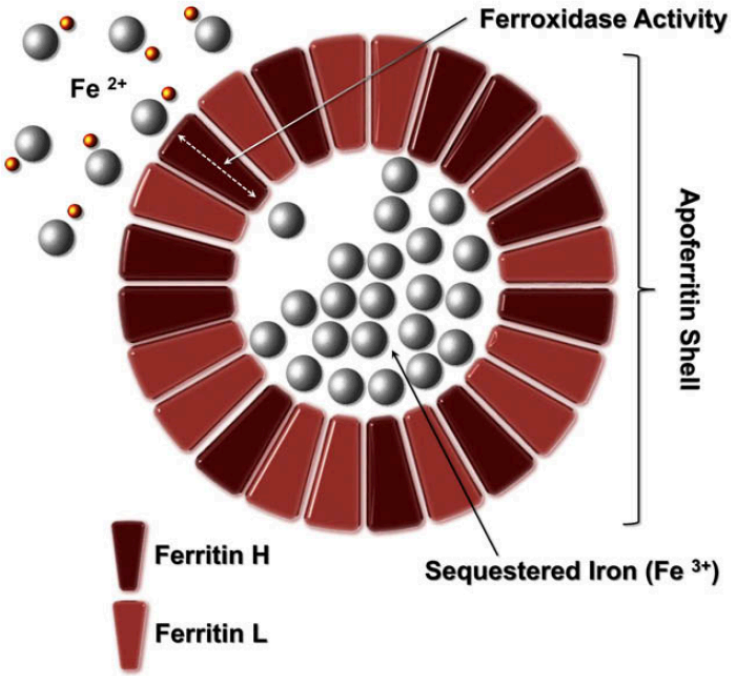
- Variabile da laboratorio a laboratorio
- Influenzato da età, sesso e stile di vita (fumo, alcol)
  - 30–300 µg/L maschio e femmine post-menopausa
  - 15–200 µg/L femmine pre-menopausa.

Ferritin

- The major intracellular iron storage protein >> up about 4500 iron atoms.
- 2 subunits types assembling in different proportion in a 24 subunits-polymer:

- H-subunit (*Heavy, cr.11*)
  - mainly in cell cytoplasm
  - ferroxidase activity >> sequestering and detoxification of iron
  - organ of low iron content (hearth, pancreas, kidney)

- L-subunit (*Light, cr.19*)
  - also in low amount in serum
  - assist the functionality of H-subunit >> nucleation of the iron core and long-term storage
  - iron storage organs (liver and spleen)



M.A. Knovich et al./ Blood Reviews 23 (2009) 95–104

Cause e meccanismi

Ferritin regulation

The synthesis is regulated by:

- **intracellular iron** (IRP/IRE on FT mRNA)
- **cytokines** (TNFα, IL1α, IL1β, IL6)
- **oxidative stress**
- **hypoxia-ischemia, and hyperoxia** (NO)
- **hormones** (thyroid hormone, insulin)
- **growth factors** (IGF-1)

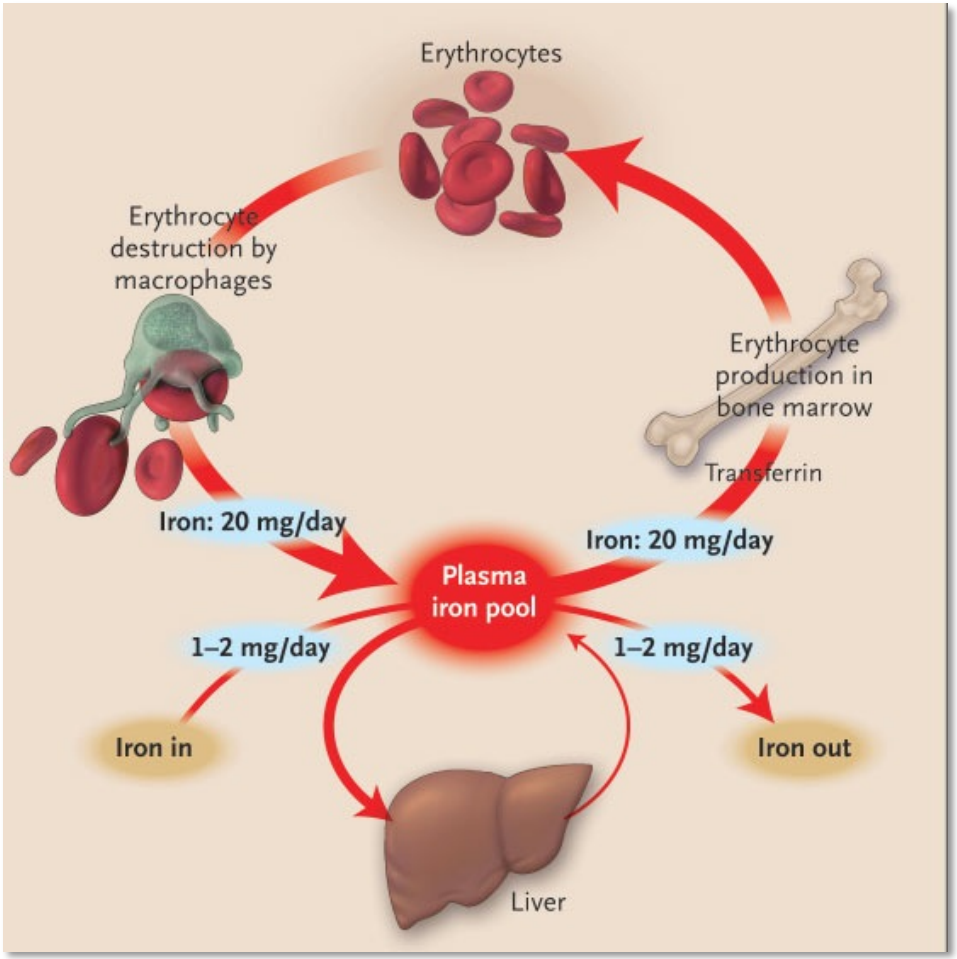
Cause acquisite

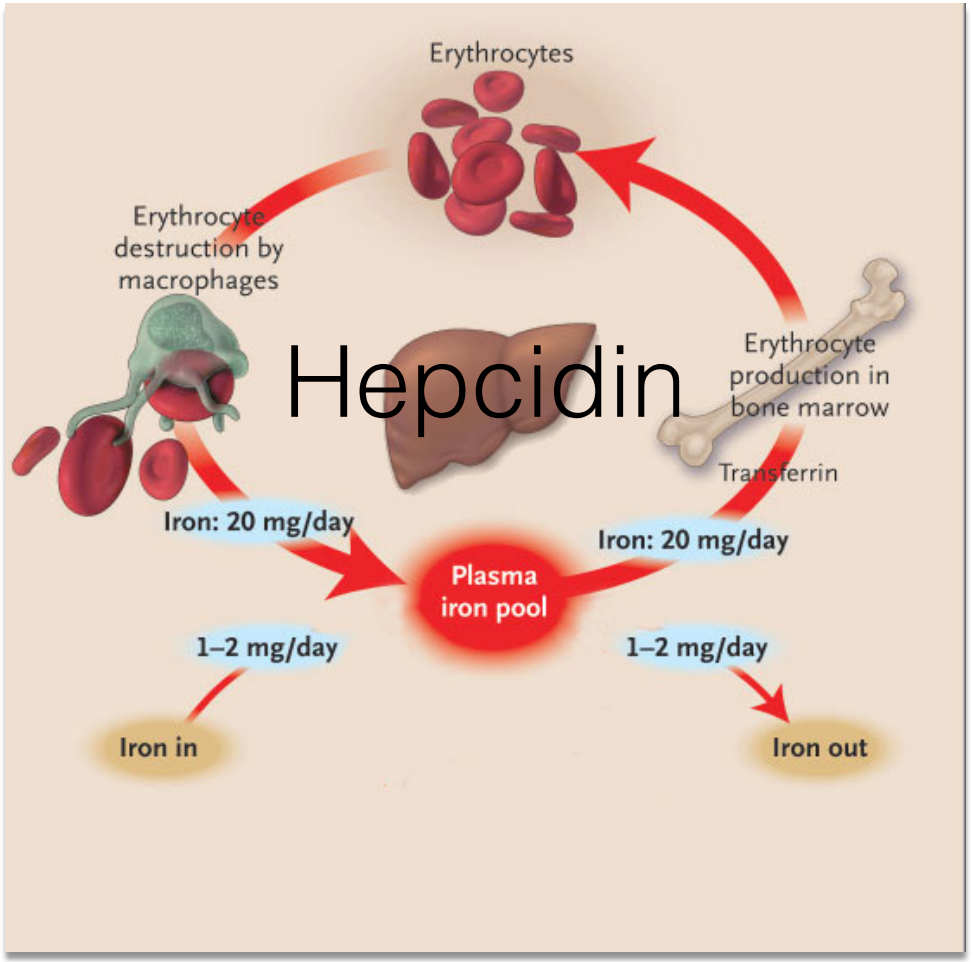
- Disordini infiammatori cronici
- Epatopatie croniche
  - Alcol
  - Virali
  - NAFL/NASH
- Sindrome Metabolica
- Malattie ematologiche
- Sovraccarico orale o parenterale

Cause genetiche

- Emocromatosi ereditaria
  - HFE correlata
  - Non HFE correlata
- Malattia della Ferroportina
- Anemie ereditarie con eritropoiesi inefficace/necessità di supporto trasfusionale
- Iperferritinemie ereditarie: *iperferritinemia e cataratta, iperferritinemia benigna*
- Aceruloplasminemia
- M. di Gaucher
- Atransferrinemia
- Deficit di DMT1

Patogenesi e fisiopatologia



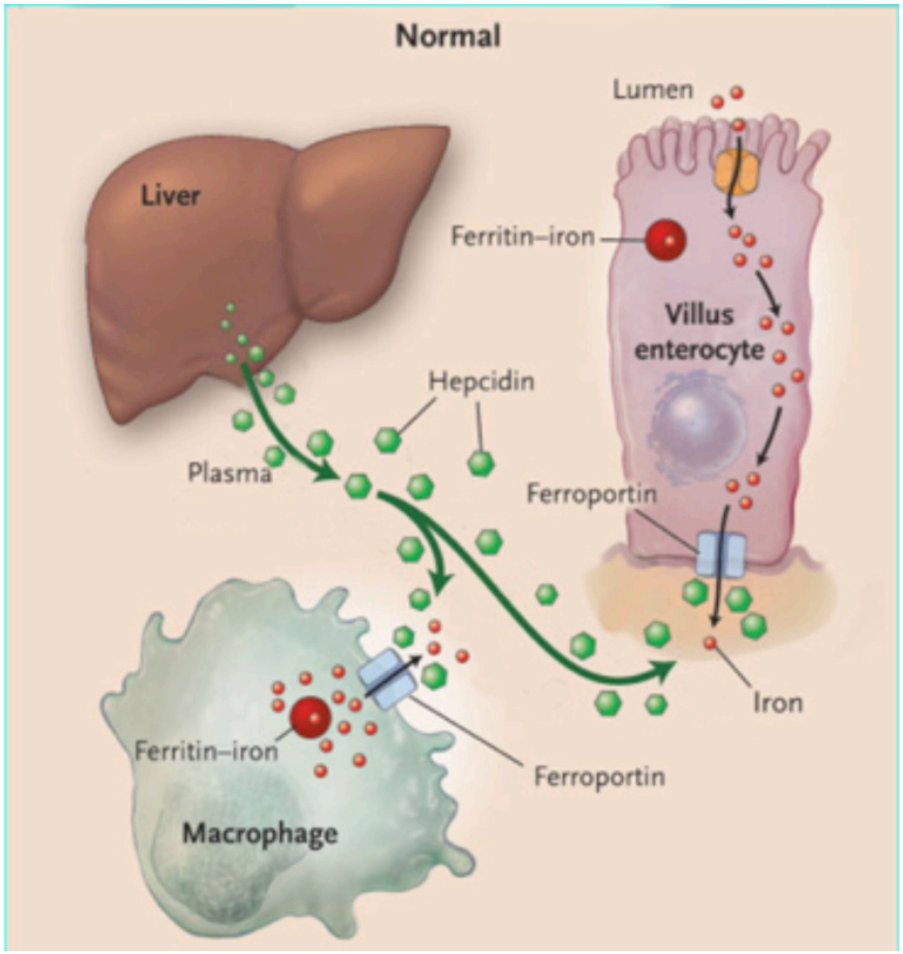


A. Pietrangelo, N Engl J Med, 350, 2383-7, 2004

Patogenesi e fisiopatologia

L'anemia da infiammazione cronica

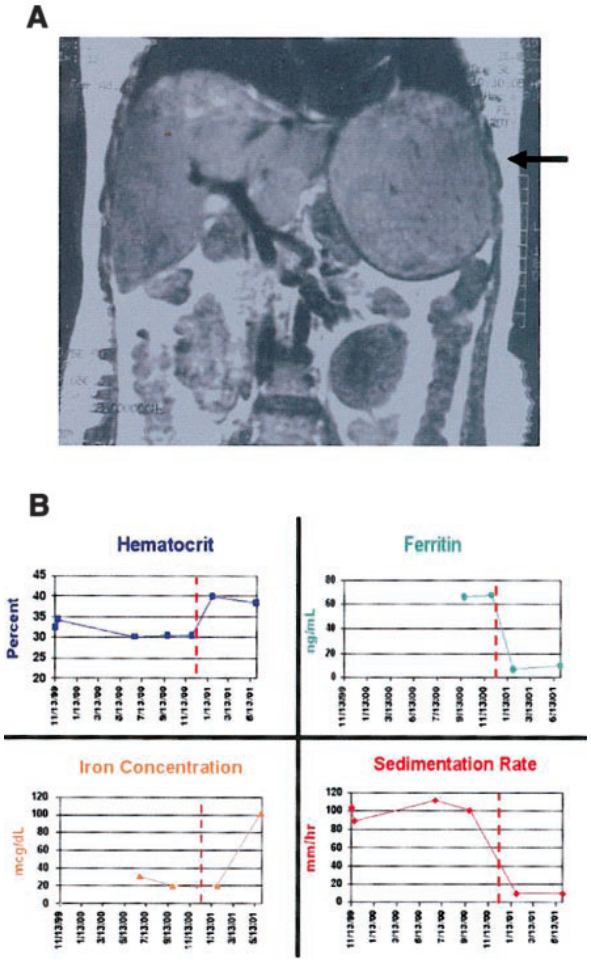
L'asse epcidina-ferroportina



A. Pietrangelo. 2004. New Engl J Med

L'anemia da infiammazione cronica

- Malattie reumatiche
- Malattie infiammatorie intestinale
- Insufficienza renale
- Cancro
- ….

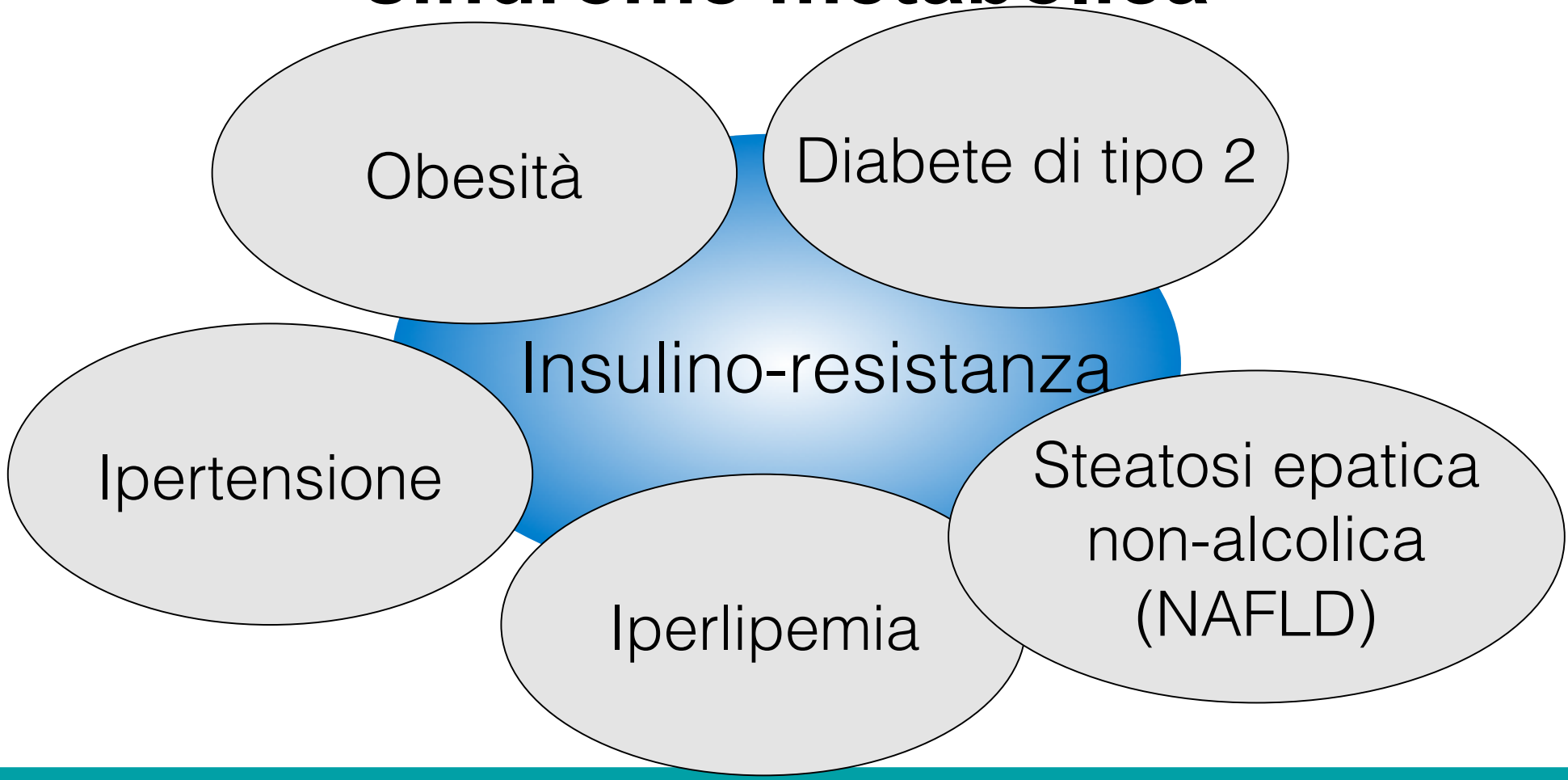


Weinstein et a. Blood 2002

Patogenesi e fisiopatologia

Malattie metaboliche ed epatopatie croniche

Iperferritinemia, diabete e sindrome metabolica

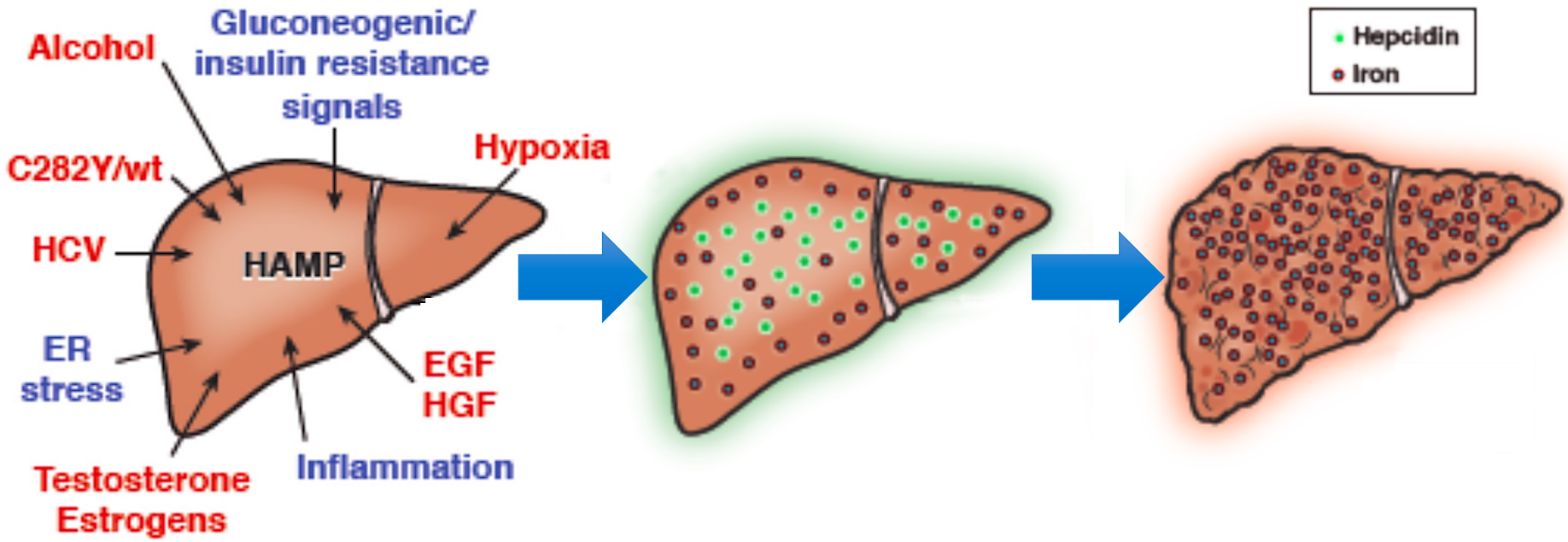


Iron, diabetes and insulin resistance in the general population

- In the general population, body iron stores are positively associated with the development of glucose intolerance, type 2 diabetes (T2D)
- In U.S., men with newly diagnosed diabetes: OR of 4.94 and women of 3.61 of having elevated ferritin concentrations.
- In Europe, US (9486), in Asia (32,826) hyperferritinemia -> higher risk to develop T2D. In the HEIRS study, 97,470 subjects belonging to six ethnic groups, ferritin was independently associated with T2D

Medalie JH, et al. Arch Intern Med 135:811–817, 1975; Wilson PW, et al. Am J Epidemiol 114:697–704, 1981; Catalano C, et al. Diabetes 45:576–579, 1996; Salonen JT, et al. Br Med J 317:727–730, 1999; Ford ES, et al. Diabetes Care 22:1978–1983, 1999; Barbieri M, et al. Diabetologia 44:1232–1237, 2001; Jiang R, et al. JAMA 2004;291:711–717; Acton RT, et al. Diabetes Care 2006;29:2084–2089

Chronic liver disease: hepcidin modulation



Intrahepatic hepcidin modulation due to toxins and disease-related factors

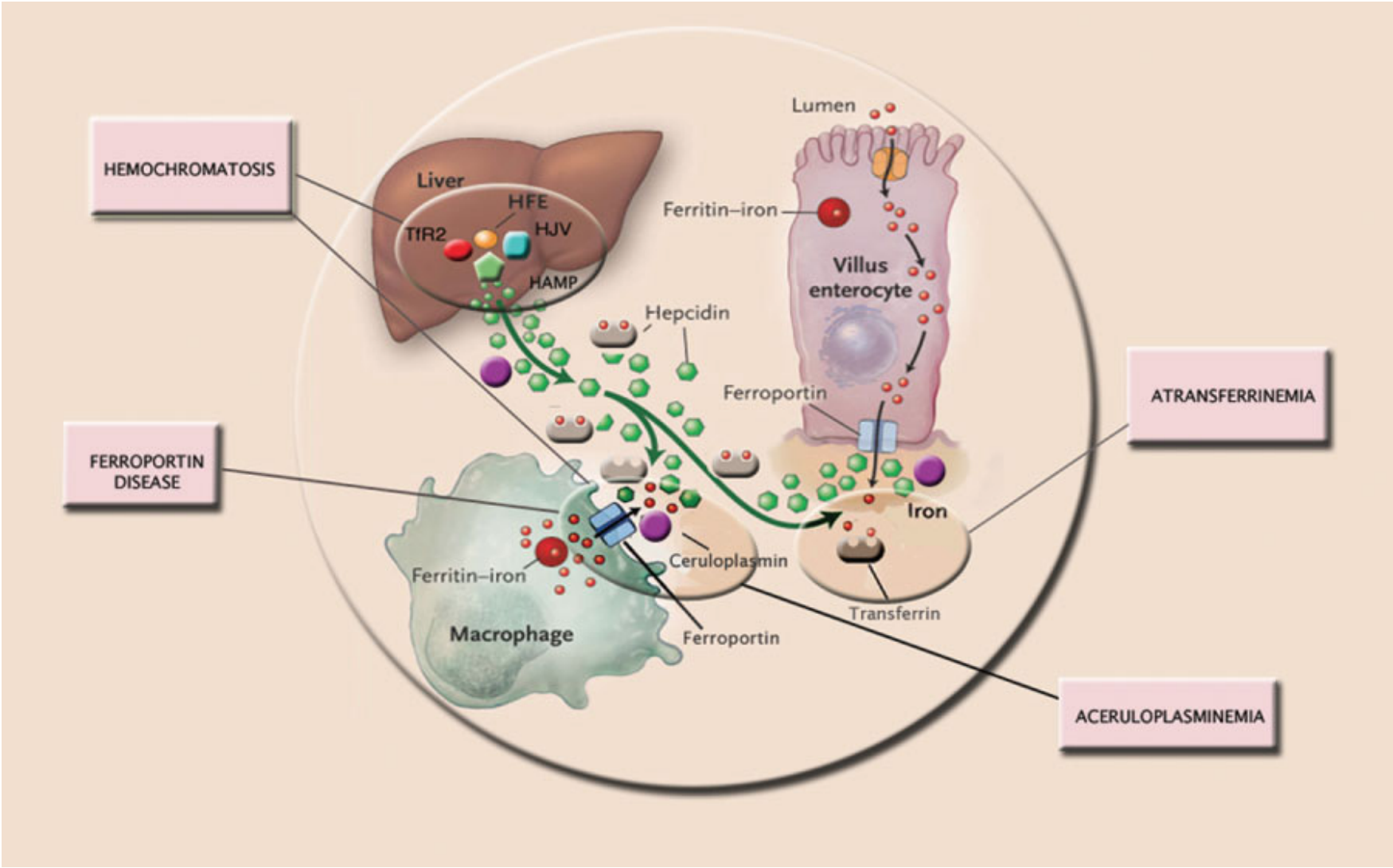
Paracrine /endocrine effects on Intrahepatic Iron traffic and deposition

Accelerated liver disease through iron co-factorial toxicity

A. Pietrangelo, Gastroenterology, 149: 1240-1251, 2015

Patogenesi e fisiopatologia

L'emocromatosi e altre malattie ereditarie



A. Pietrangelo, HEPATOLOGY 2007;46:1291-1301

Iperferritinemia: Concetti chiave

- Molto comune nella attività clinica quotidiana
- Diverse cause
- Frequente, ma raremente dovuta a reale sovraccarico di ferro
- Usualmente legata a condizioni dismetaboliche e/o infiammatorie
- L'epcidina è spesso coinvolta nella patogenesi
  - Attivata nelle forme secondarie/acquisite
  - Deficitaria nelle forme congenite più frequenti (emocromatosi)