Sobrecàrrega de ferro i infeccions

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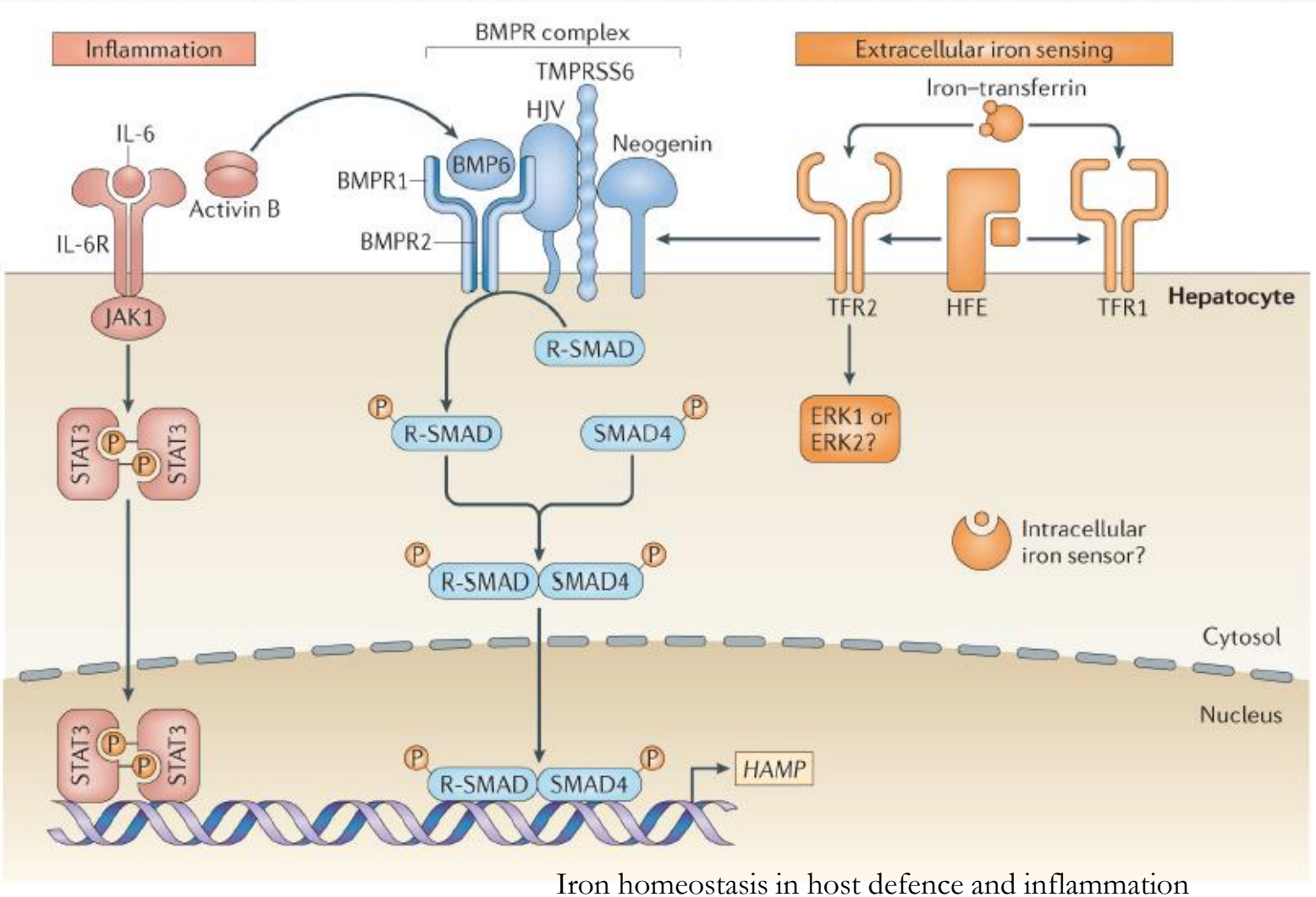
Cap de Servei Hematologia Althaia

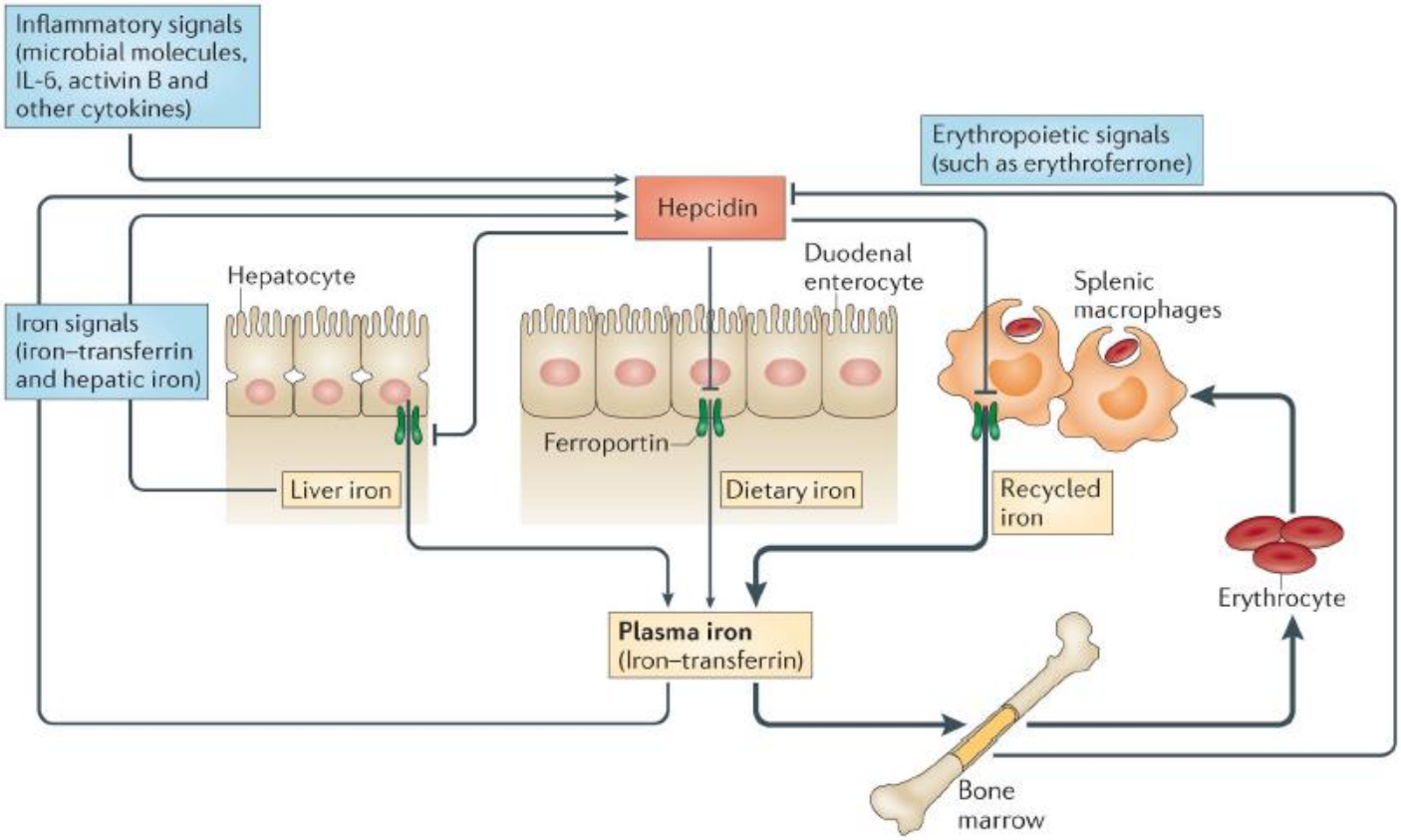
V Curs eritropatologia SCHH 9/11/2017

Situacions amb sobrecàrrega de ferro i susceptibilitat a la infecció

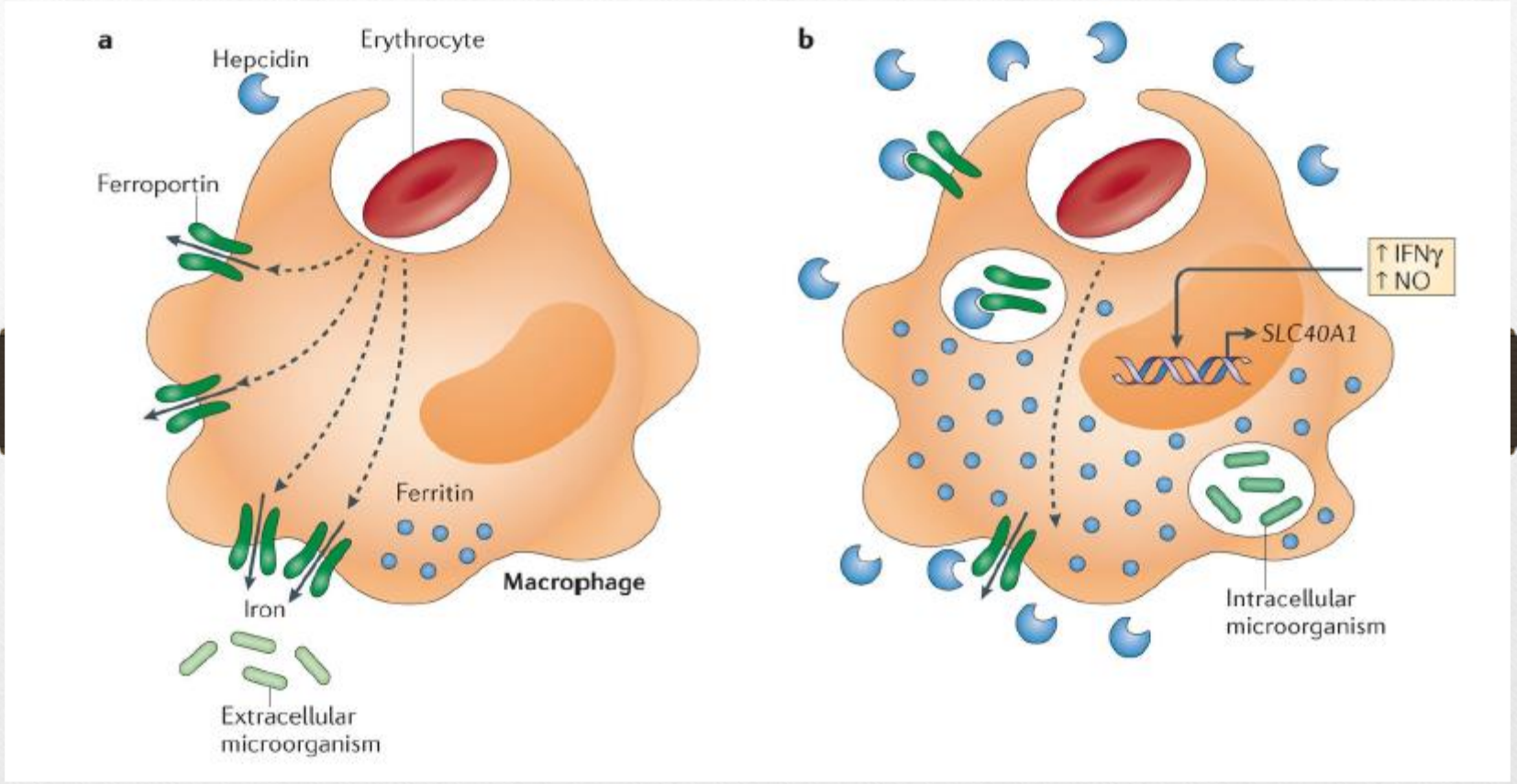
- Anèmies congènites amb sobrecàrrega
  - Beta talassèmia
  - Hemolítiques cròniques (falciforme, esferocitosi, ...)
  - Anèmia congènita diseritropoiètica, sideroblàstica.
- Anèmies adquirides amb politransfusió
  - Síndromes mielodisplàssiques
  - Trasplantament de moll d'òs
- Ús inadequat de ferro parenteral
  - Insuficiència renal
- Hemocromatosi hereditària



Iron homeostasis in host defence and inflammation
T. Ganz and E Nemeth. Nat Rev Immunol 2015;15:500-510



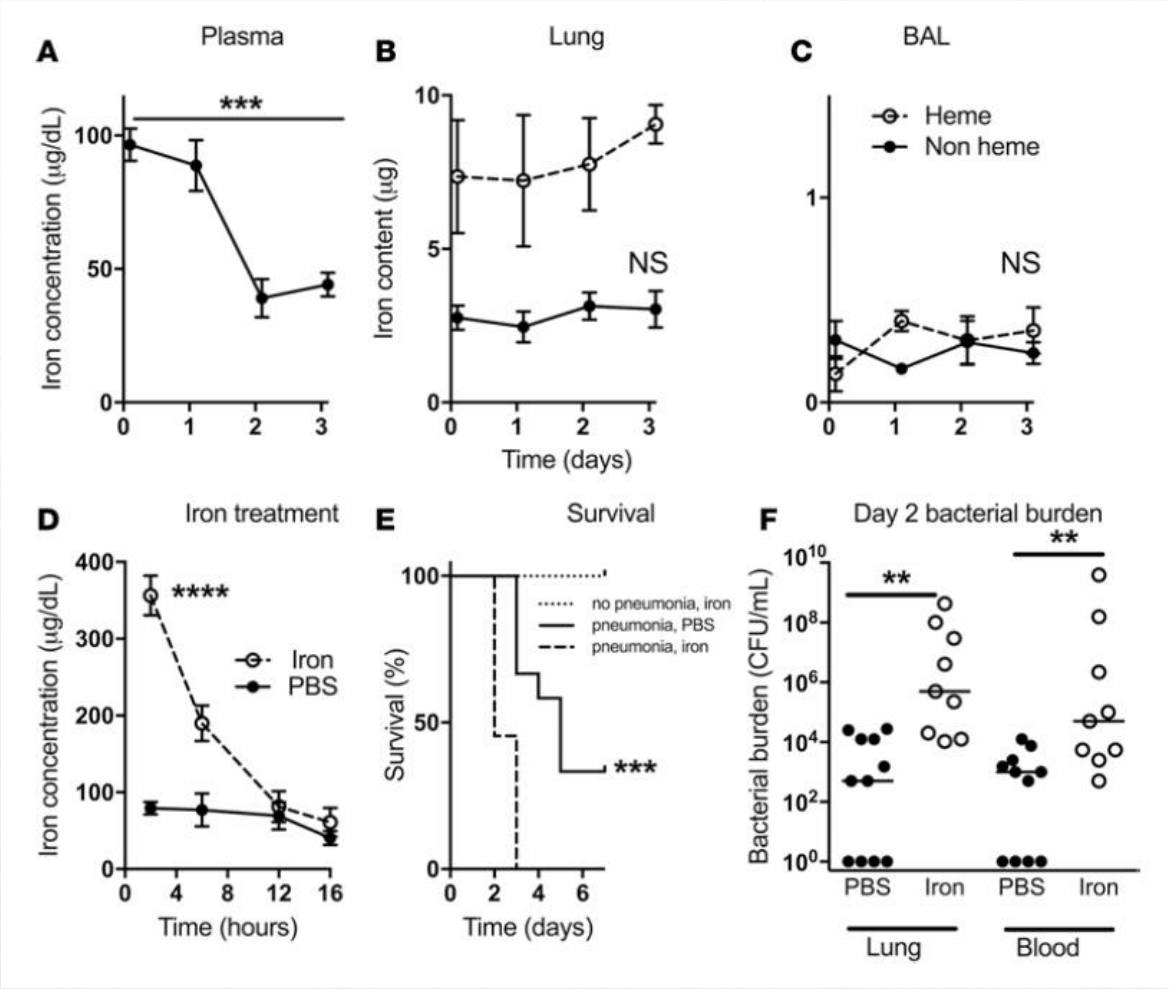
Iron homeostasis in host defence and inflammation
T. Ganz and E Nemeth. Nat Rev Immunol 2015;15:500-510



Iron homeostasis in host defence and inflammation
T. Ganz and E Nemeth. Nat Rev Immunol 2015;15:500-510

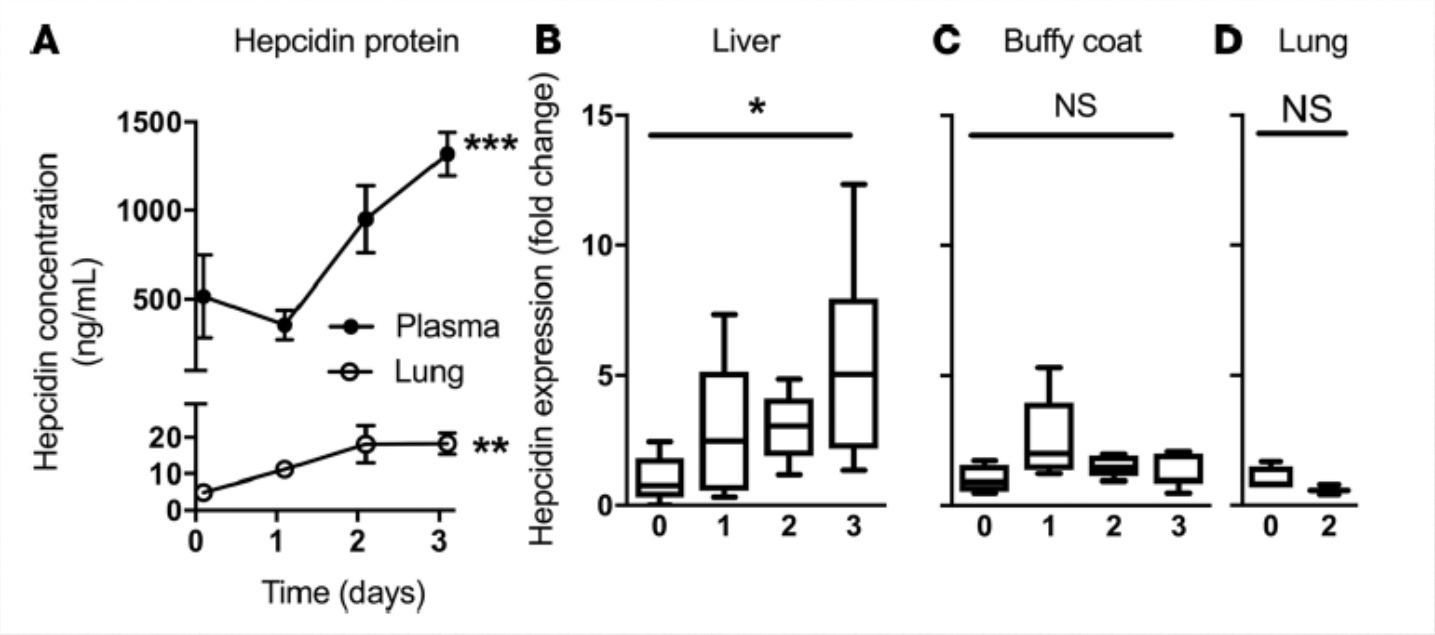
Això son models teòrics però…

Que passa realment "*in vivo*"?

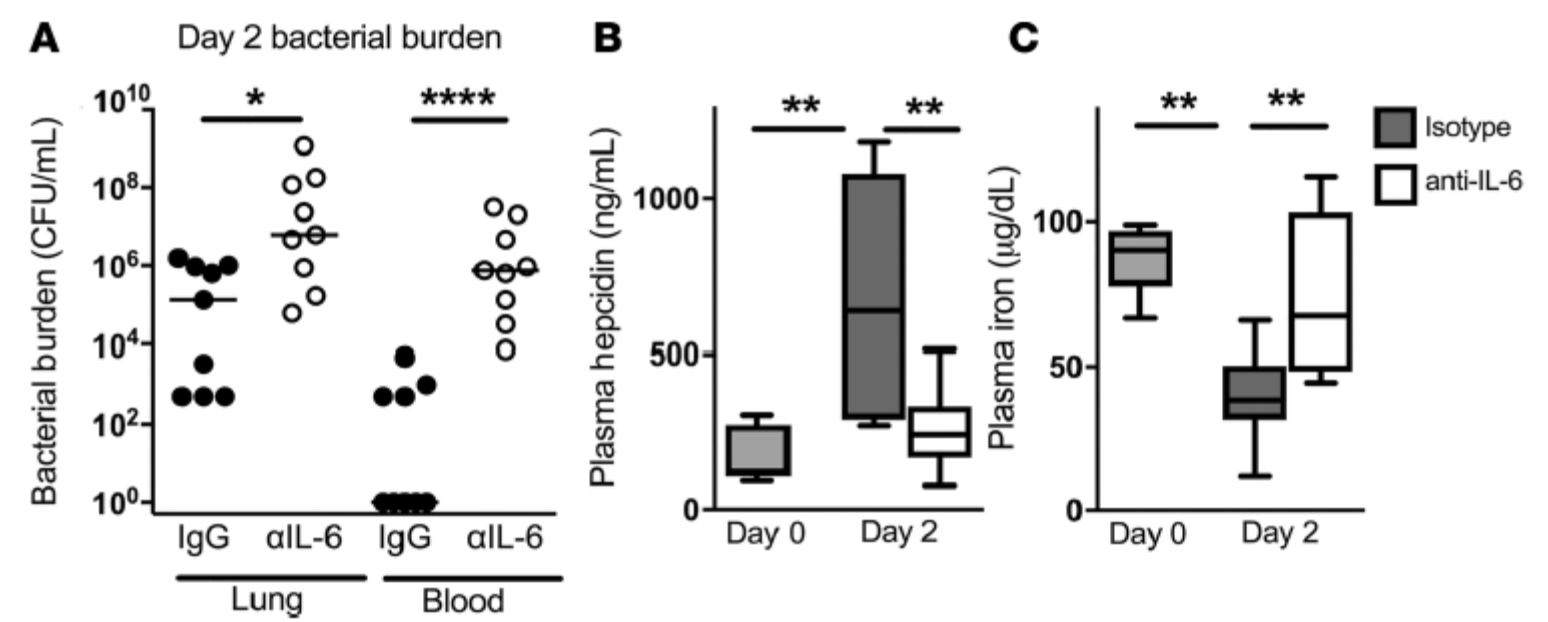


Model ratolí – Klebsiella pn. a la traquea

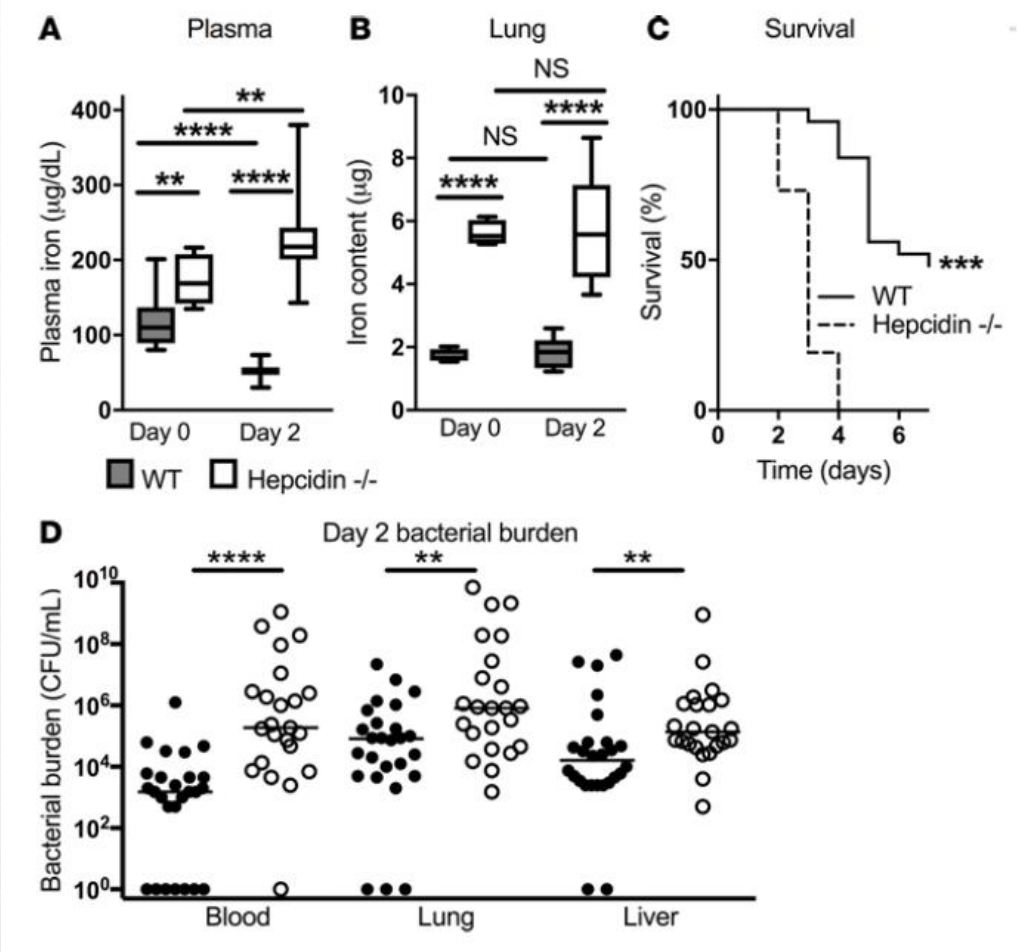
Michels KR et al. JCI insight 2017



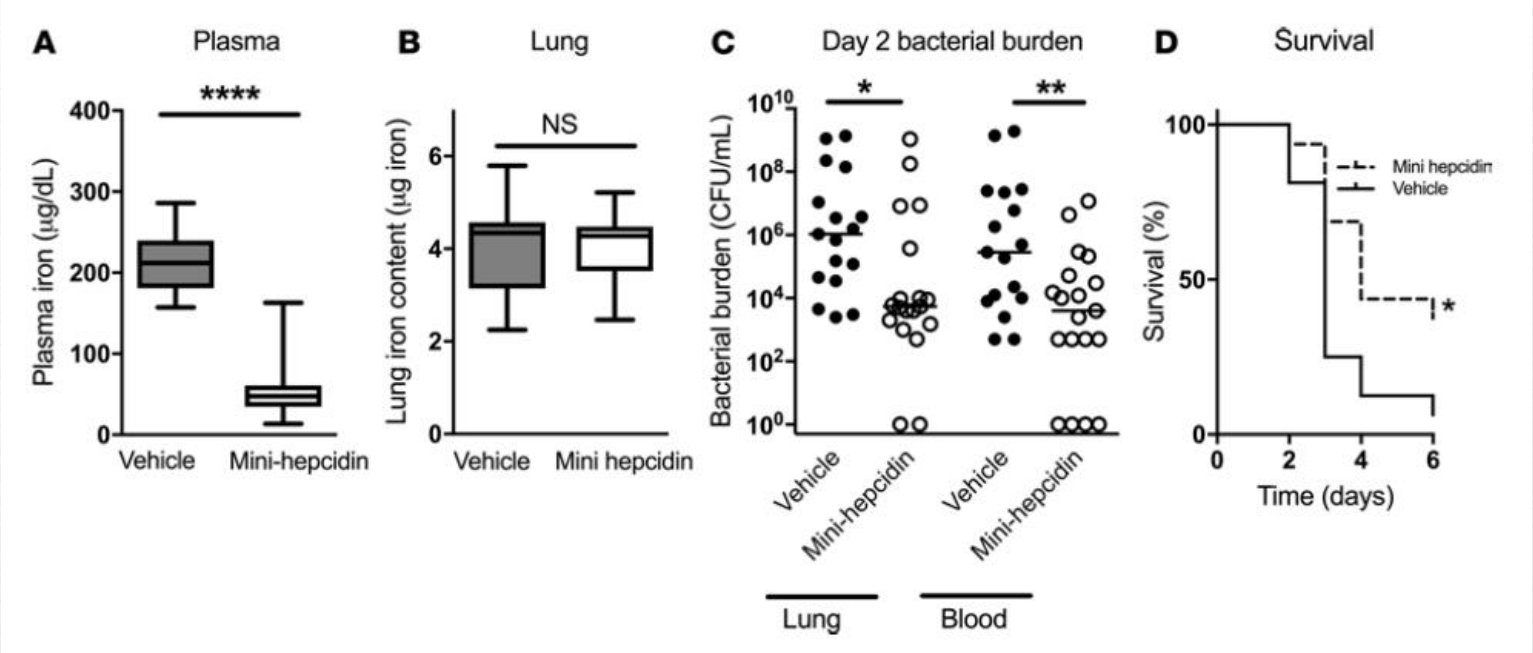
Michels KR et al. JCI insight 2017



Michels KR et al. JCI insight 2017



Michels KR et al. JCI insight 2017



Michels KR et al. JCI insight 2017

This work has several implications for future research. First, our results may have implications for the therapeutic use of hepcidin antagonists, which are currently under development for the treatment of anemia of inflammation. In this context, we posit that relieving the iron-restricted state could predispose some individuals to Gram-negative sepsis. Second, impaired hepcidin production is a feature of several common clinical entities, including alcohol intoxication and chronic liver disease (33–36), illnesses associated with striking susceptibility to Gram-negative bacteremia (51, 52). Our data suggest that impaired hepcidin production may represent an unappreciated mechanism predisposing these hosts to infection. Finally, hepcidin agonists may represent a novel therapeutic strategy in illnesses where hepcidin production is diminished, such as liver disease and hereditary hemochromatosis, and possibly more broadly in acquired iron-overload states.

Concepte de "iron – targeted nutritional immunity"

Aquest tipus de resposta preveu la superinfecció per paràsits de malaria addicionals en subsegüents picades de mosquits infectats

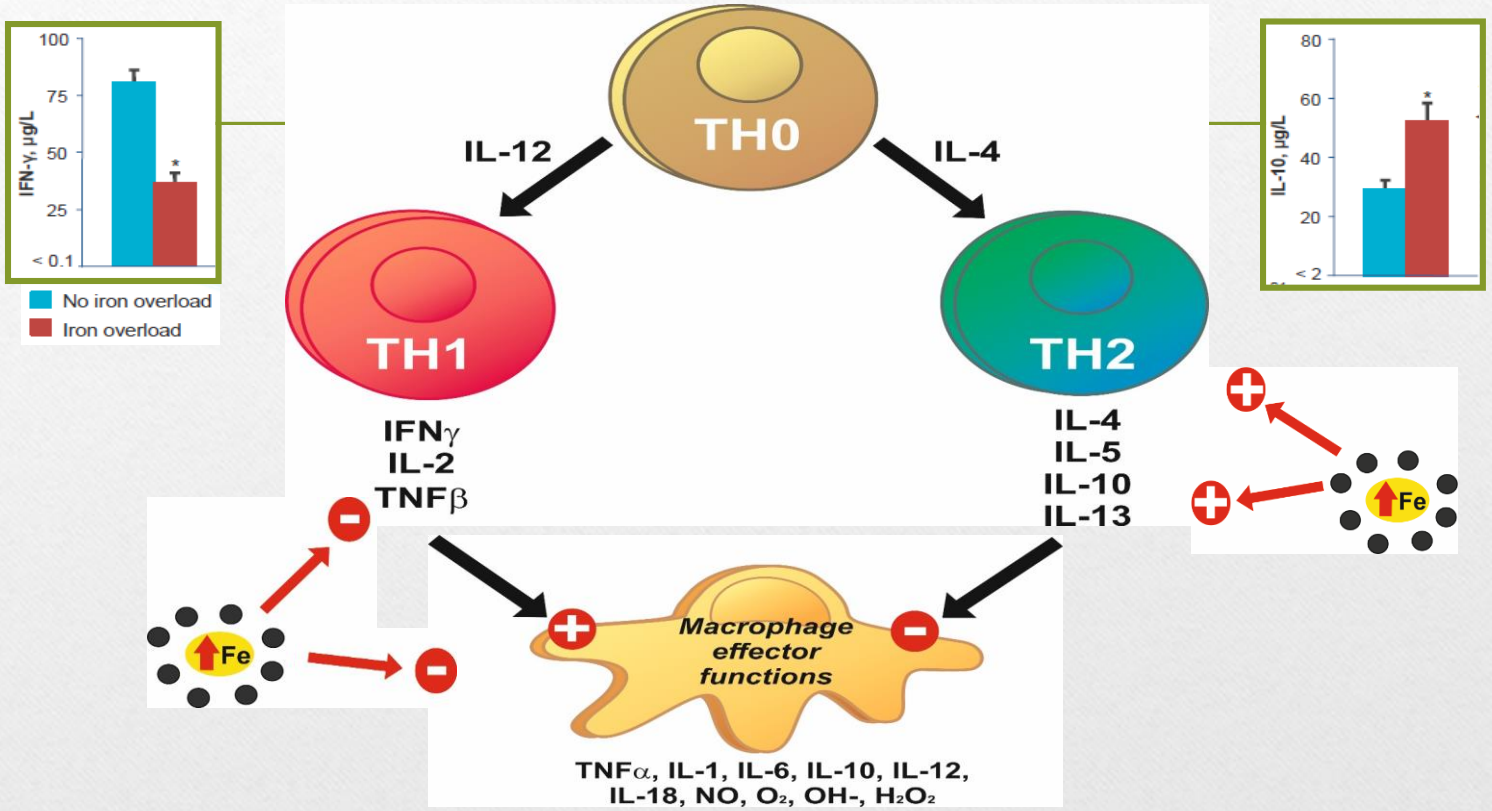
Iron homeostasis in host defence and inflammation
T. Ganz and E Nemeth. Nat Rev Immunol 2015;15:500-510

Infections associated with genetic iron overload

Although the relative risk has not yet been estimated, it is clear that patients with hereditary haemochromatosis are predisposed to otherwise rare infections with two Gram-negative bacterial species: the marine organism *Vibrio vulnificus*[42] (and related *Vibrio* species) and the largely zoonotic bacterium *Yersinia enterocolitica*[43,44]. In several reported cases, lethal infections with siderophilic bacteria developed before haemochromatosis was diagnosed[44–46]. In a particularly poignant case, a researcher with latent hereditary haemochromatosis died rapidly after exposure to a laboratory strain of *Yersinia pestis*[45] that was thought to be attenuated because it lacked yersinia-bactin, which is a siderophore required for efficient iron uptake. The pathogenicity of similar strains was greatly enhanced

Iron homeostasis in host defence and inflammation
T. Ganz and E Nemeth. Nat Rev Immunol 2015;15:500-510

Efecte de la sobrecàrrega fèrrica en el balanç Th1/Th2



IFN, interferon; IL, interleukin; TH1/Th2; T helper cell 1/2; TNF, tumor necrosis factor

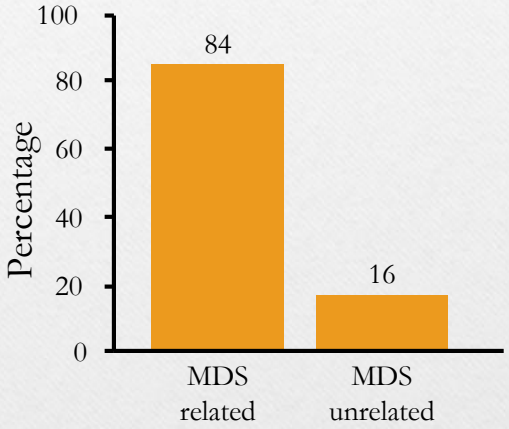
Weiss G *et al. Immunol Today* 1995;16:495–500;
Mencacci A *et al. J Infect Disease* 1997;175:1467–1476

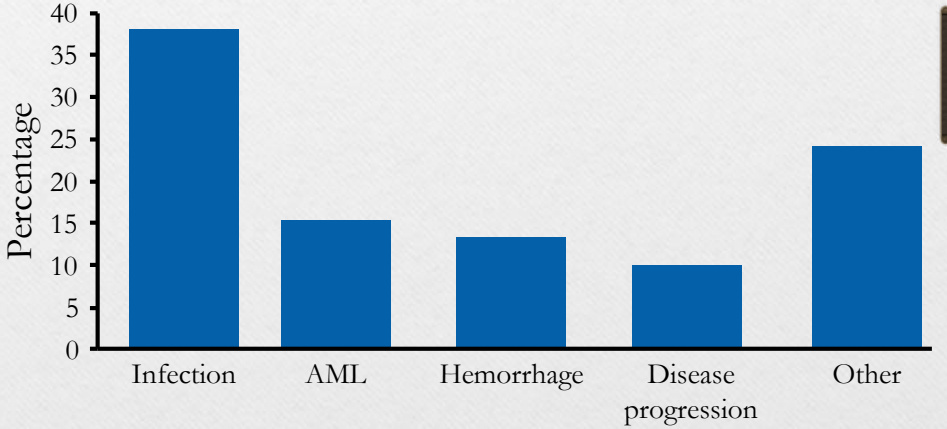
- Els pacients amb hemocromatosi i baixa producció d'hepcidina podrien estar "protegits" de infeccions per germens intracelulars

- Els pacients amb sobrecàrrega férrica macrofàgica podrien ser susceptibles de infeccions intracelulars

Les infeccions són una causa freqüent de mort en els SMD de baix/intermig risk

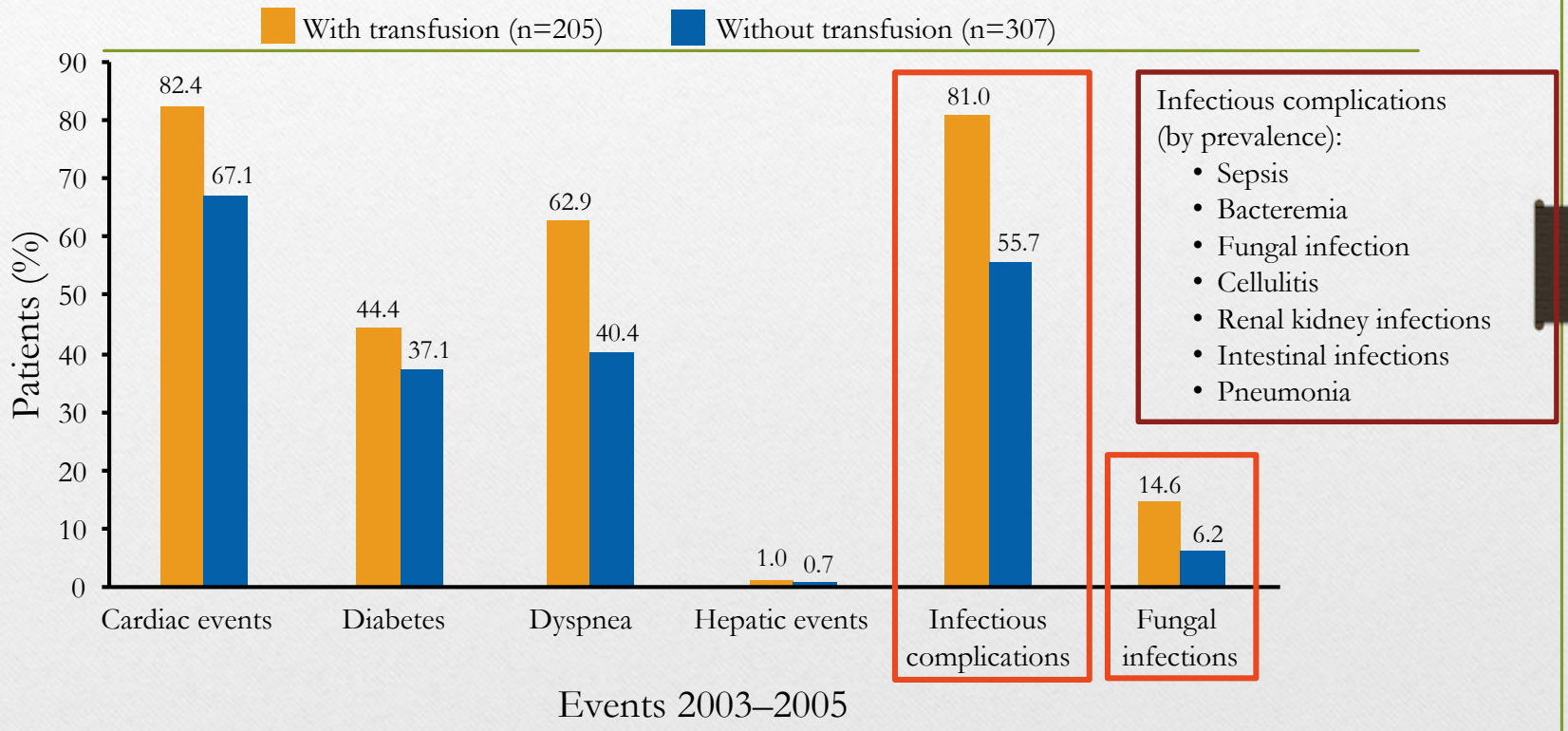
273 patients with Low/Int-1 risk MDS who received supportive care only (transfusions and growth factor)





Dayyani F *et al. Cancer* 2010;116:2174–2179

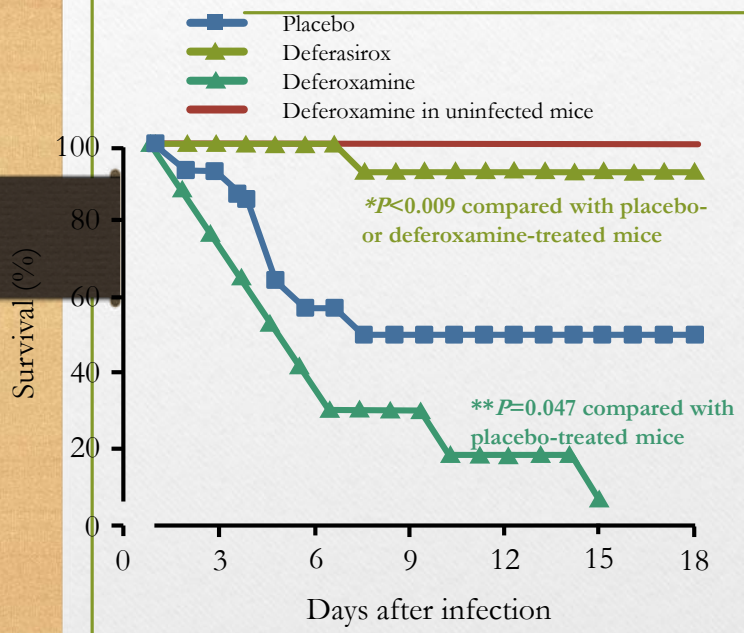
Les complicacions infeccioses són comorbiditats prevalens en els pacients amb SMD transfusió-depenent



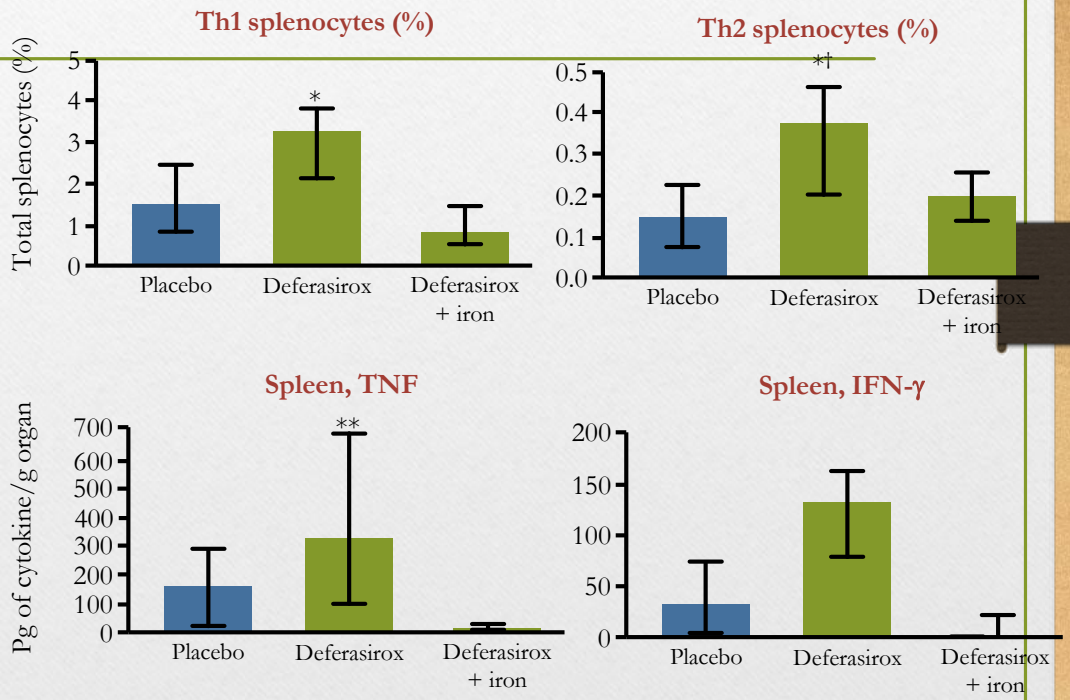
Goldberg S *et al. J Clin Oncol* 2010;28:2847–2852

Supervivència i resposta immune segons tractament amb deferasirox en models pre-clinics

Survival of diabetic ketoacidotic mice infected with *Rhyzopus oryzae*



Immune system response after *Rhyzopus oryzae* infection



*P<0.02 compared with placebo or deferasirox plus ferric chloride;
**P<0.05 and †P<0.07 compared to deferasirox plus ferric chloride

Ibrahim AS *et al. J Clin Invest* 2007;117:2649–2657

EXPERT REVIEWS

Toward resolving the unsettled role of iron chelation therapy in myelodysplastic syndromes

Expert Rev. Anticancer Ther. 14(7), 817–829 (2014)

discussed. Although suggested by retrospective analyses, the lack of clear prospective data of the beneficial effects of iron chelation on morbidity and survival, the role of iron chelation therapy in MDS patients remains controversial.

Myelodysplastic Syndromes (MDS) Event Free Survival With Iron Chelation Therapy Study (TELESTO)

This study is ongoing, but not recruiting participants.

Sponsor:
Novartis Pharmaceuticals

ClinicalTrials.gov Identifier:
NCT00940602

First Posted: July 16, 2009
Last Update Posted: September 12, 2017

Study Status:	This study is ongoing, but not recruiting participants.
Estimated Study Completion Date:	February 2, 2018
Estimated Primary Completion Date:	February 2, 2018 (Final data collection date for primary outcome measure)

Molecular Microbiology (2014) 93(1), 10–23 ■

doi:10.1111/mmi.12653
First published online 9 June 2014

MicroReview

Iron and copper as virulence modulators in human fungal pathogens

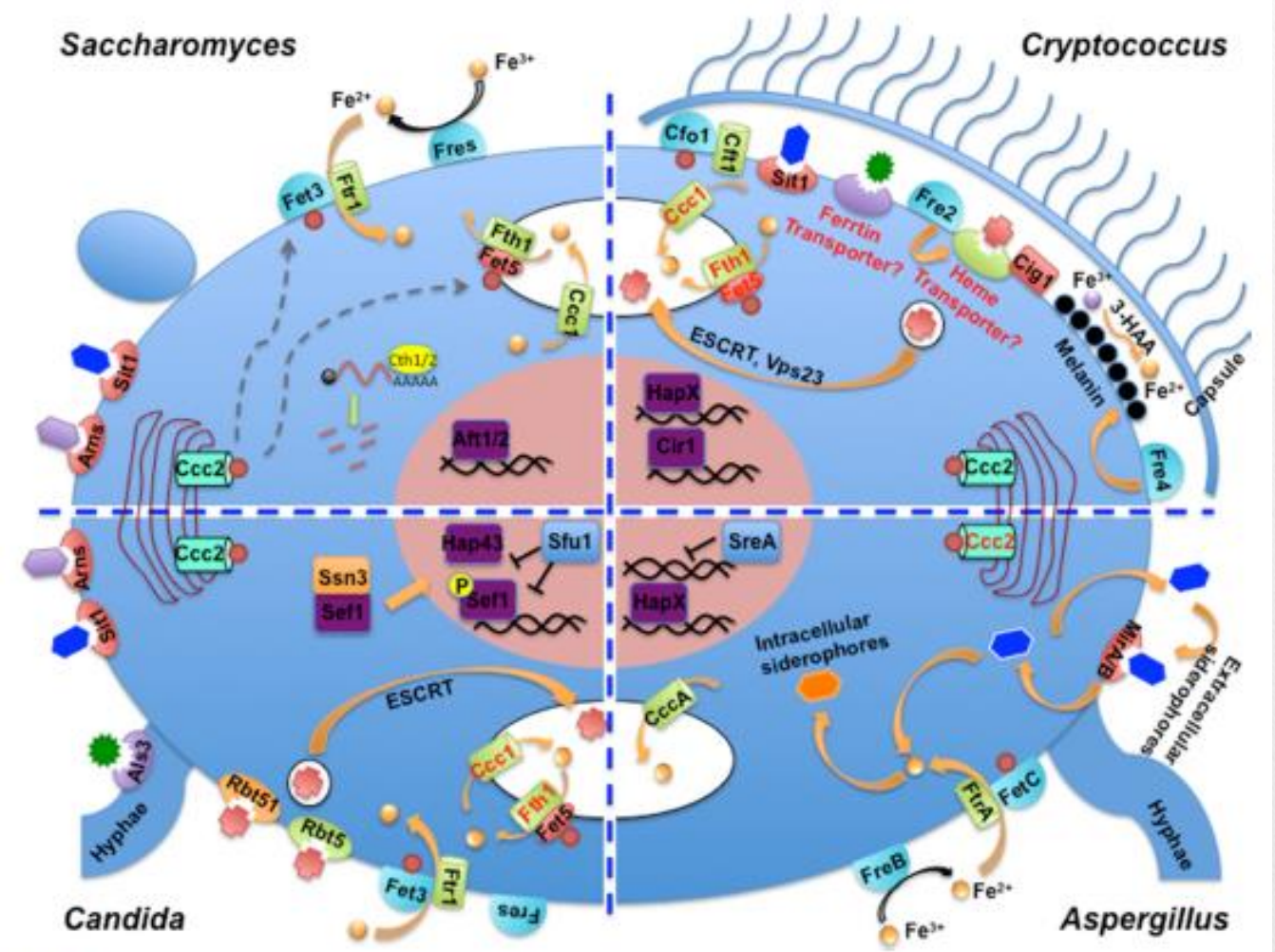


Fig. 1. Iron homeostasis in *Saccharomyces cerevisiae* and major human pathogenic fungi.

Review

EMBO reports

The Iron age of host–microbe interactions

Miguel P Soares[1,*] & Günter Weiss[2,**]

EMBO reports Vol 16 | No 11 | 2015

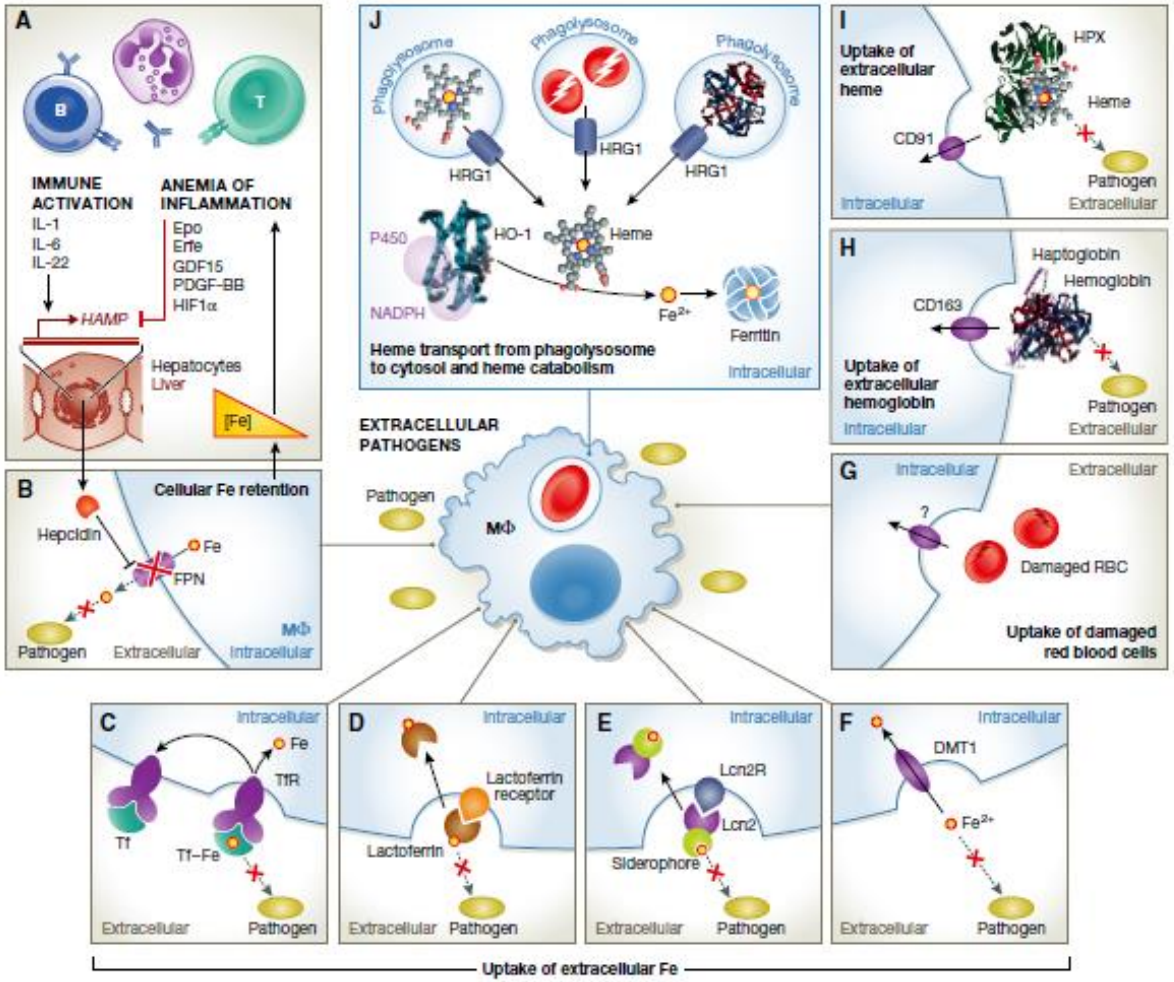
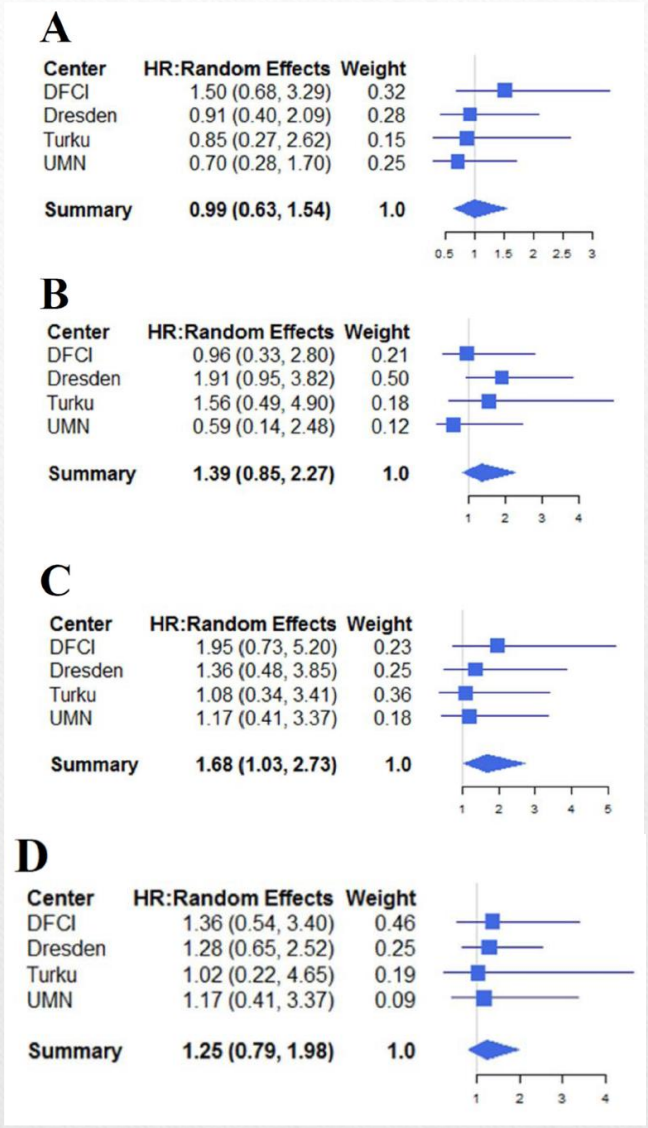


Figure 2. Regulation of Fe metabolism in response to extracellular pathogens.
(A) Immune responses to extracellular pathogens encompass the production of cytokines, for example, IL-1, IL-6, and IL-22, which induce the transcription of the

Biol Blood Marrow Transplant. 2014 August ; 20(8): 1248–1251. doi:10.1016/j.bbmt.2014.04.024.

Iron Overload in Allogeneic Hematopoietic Cell Transplantation Outcome: A Meta-Analysis

Philippe Armand, MD, PhD[1], Haesook T. Kim, PhD[2], Johanna M. Virtanen, MD[3], Riitta K. Parkkola, MD, PhD[3], Maija A. Itälä-Remes, MD, PhD[4], Navneet S. Majhail, MD, MS[5], Linda J. Burns, MD[6], Todd DeFor, MS[7], Bryan Trottier, MD[6], Uwe Platzbecker, MD[7], Joseph H. Antin, MD[1], and Martin Wermke, MD[7]



LIC > 5 mg/gdw

LIC > 7 mg/gdw

Ferritina > 1000

Ferritina > 2500

Published in final edited form as:
Semin Dial. 2014 ; 27(1): 26–36. doi:10.1111/sdi.12168.

Iron and Infection in Hemodialysis Patients

Julie H. Ishida[1] and **Kirsten L. Johansen**[1,2,3]

Ferritin and Infection in Hemodialysis Patients

Thirteen studies with sample sizes ranging from 61 to 2,662 have examined the link between serum ferritin and infection in hemodialysis patients (Table 1). Nine of these studies found that high serum ferritin (typically defined as >500 or 1,000 ng/mL or, equivalently, μg/L) was associated with higher incidence of bacterial infection or infection-related mortality (11,13,28,53–58). The incidence of bacterial infection ranged from 0.34 to 0.59 infections per patient-year (in studies evaluating the rate of infection) and 0.93% to 61.9% (in studies evaluating the proportion with infection) in the higher serum ferritin groups and 0.09 to 0.18 infections per patient-year and 0% to 37% in the lower serum ferritin groups (13,28,53–56,58). In absolute terms, these studies suggest an excess of 16 to 50 infections per 100 patient-years in the higher compared with the lower serum ferritin groups. In studies that expressed the association between serum ferritin and bacterial infection as ratios, higher serum ferritin was independently associated with a 1.5 to 3.1-fold higher incidence of bacterial infection or infection-related mortality (11,28,57,58).

Iron Usage and Infection in Hemodialysis Patients

Twenty-four studies have evaluated the association between iron usage and infection in hemodialysis patients (Table 2). While not the primary aim of the analyses, two randomized-controlled studies have addressed the association between any iron usage or more "aggressive" iron repletion and infection in hemodialysis patients. In the Dialysis Patients'

BMJ 2013;347:f4822 doi: 10.1136/bmj.f4822 (Published 15 August 2013)

RESEARCH

Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials


OPEN ACCESS

Edward Litton *staff specialist clinical senior lecturer*[1 2], Jing Xiao *registrar*[1], Kwok M Ho *staff specialist associate professor*[1 3]

Conclusions Intravenous iron therapy is effective in increasing haemoglobin concentration and reducing the risk of allogeneic red blood cell transfusion and could have broad applicability to a range of acute care settings. This potential benefit is counterbalanced by a potential increased risk of infection.