



Innere Medizin IV
Nephrologie und Hypertensiologie



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

EFFECTS OF IRON ON THE IMMUNE SYSTEM

Gert Mayer

Department of Internal Medicine IV
(Nephrology and Hypertension)

Medical University Innsbruck
Austria



Conflicts of interest

Research Support: Amgen, Roche, Takeda, Ratiopharm

Honoraria: Amgen, Roche, Takeda, Medice, Astro Pharma, Ratiopharm



INTERACTION BETWEEN INFECTION / INFLAMMATION AND IRON METABOLISM

EFFECTS OF IRON SUPPLEMENTATION DURING INFECTION / INFLAMMATION

EFFECTS OF IRON SUPPLEMENTATION ON THE IMMUNE SYSTEM IN THE „ABSENCE“ OF INFECTION / INFLAMMATION



INTERACTION BETWEEN INFECTION / INFLAMMATION AND IRON METABOLISM

**EFFECTS OF IRON SUPPLEMENTATION DURING INFECTION /
INFLAMMATION**

**EFFECTS OF IRON SUPPLEMENTATION ON THE IMMUNE
SYSTEM IN THE „ABSENCE“ OF INFECTION / INFLAMMATION**



Bacteria



- Growth rates of most bacteria strongly dependent on iron
- Heavy genomic investment in iron acquisition pathways
- 500+ known siderophores with exceptional iron-binding constants
- Iron genes concentrated in high-pathogenicity regions
- Iron acquisition capacity determines niche selection

KDIGO

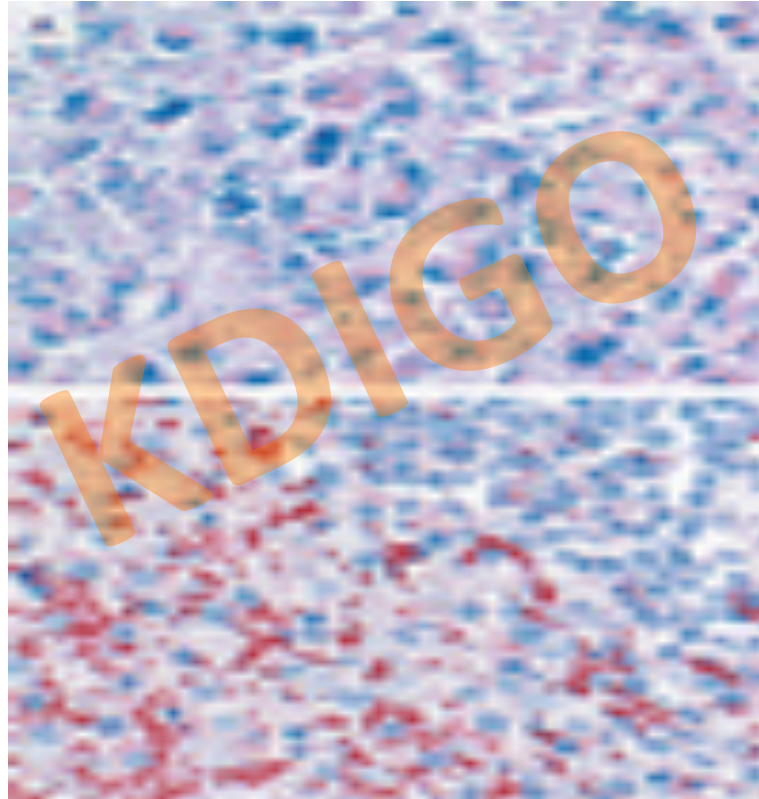


INVESTIGATION OF A RESEARCHERS DEATH DUE TO SEPTICEMIC PLAGUE BY ATTENUATED YERSINIA PESTIS

Innere Medizin IV
Nephrologie und Hypertensiologie



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK



Frank KM et al. N Engl J Med 2011

G.M. 2014



Bacteria



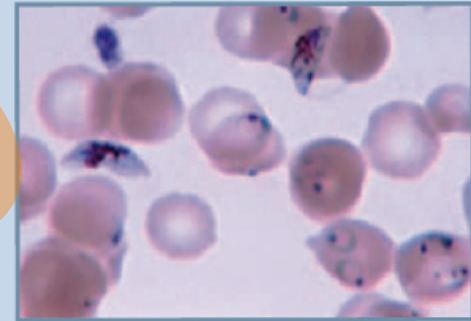
- Growth rates of most bacteria strongly dependent on iron
- Heavy genomic investment in iron acquisition pathways
- 500+ known siderophores with exceptional iron-binding constants
- Iron genes concentrated in high-pathogenicity regions
- Iron acquisition capacity determines niche selection

Viruses



- Viral replication employs iron-dependent pathways
- Some viruses use iron uptake pathways to invade cells
- High iron status strongly promotes HIV progression
- Body iron redistribution in HIV probably enhances TB risk

Protozoa



- Most evidence relates to malaria; others have been little studied
- Host iron deficiency protects against malaria infection
- Heparin-mediated hepatocyte iron depletion blocks infection
- Iron stimulates, and iron chelation limits, blood-stage growth
- Malaria-induced iron redistribution promotes bacterial co-infections



IRON CHAPERON PROTEINS ARE ACUTE PHASE REACTION PROTEINS

Innere Medizin IV
Nephrologie und Hypertensiologie



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

Lactoferrin, Transferrin, Ferritin

chaperon proteins for iron

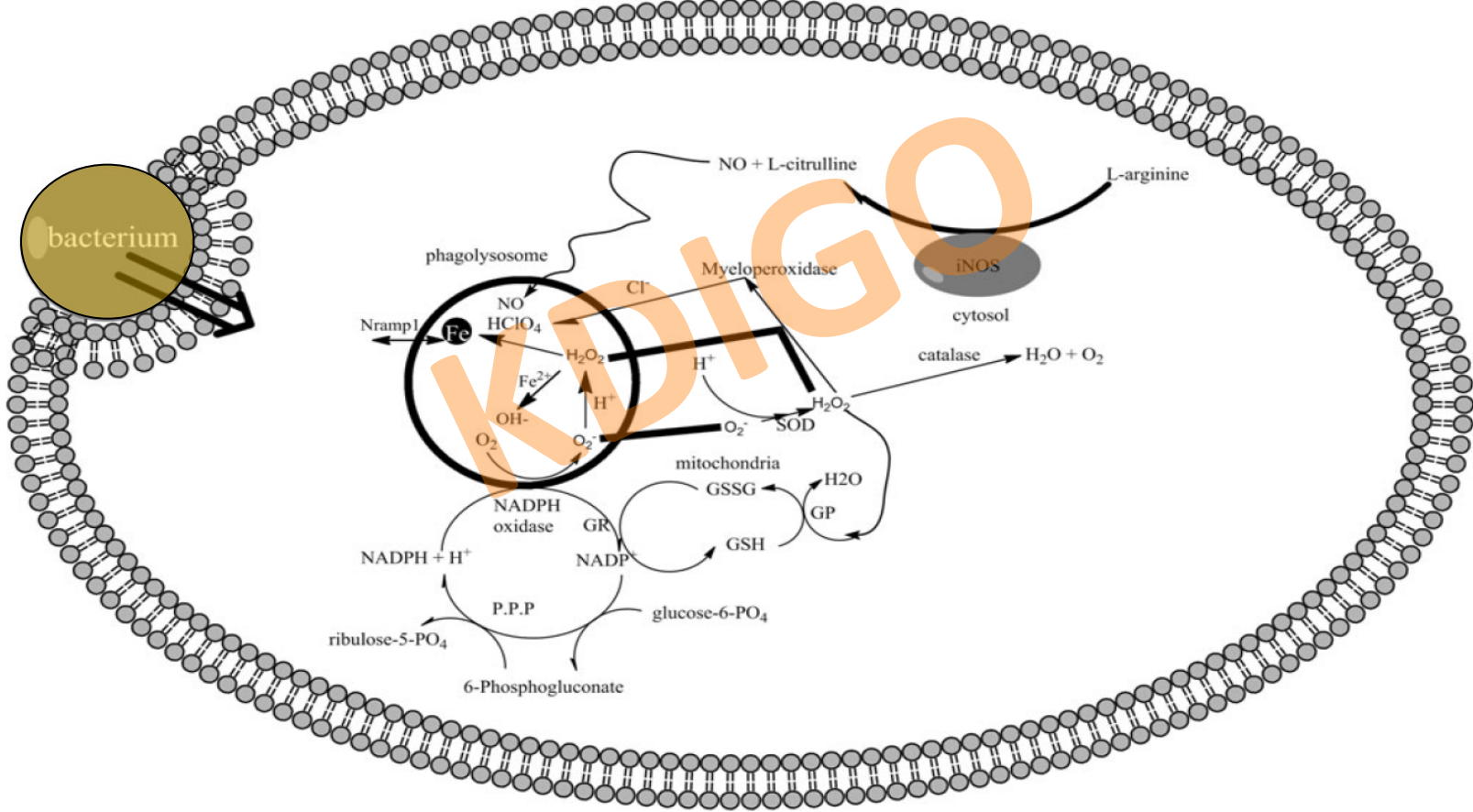
Haptoglobin

chaperon protein for hemoglobin

Hemopexin

chaperon protein for heme

KDIGO



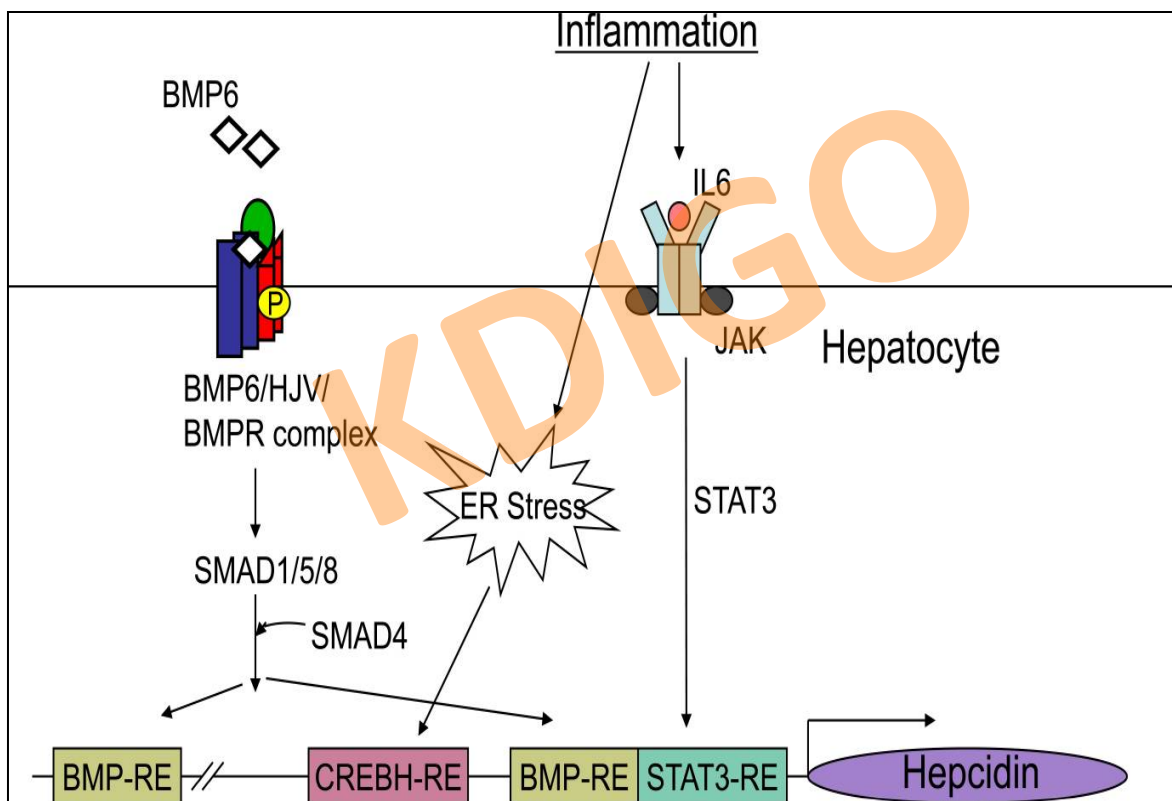


HEPCIDIN REGULATION BY IRON AVAILABILITY AND INFLAMMATION

Innere Medizin IV
Nephrologie und Hypertensiologie



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK



Babitt JL et al. Am J Kidney Dis 2010

G.M. 2014

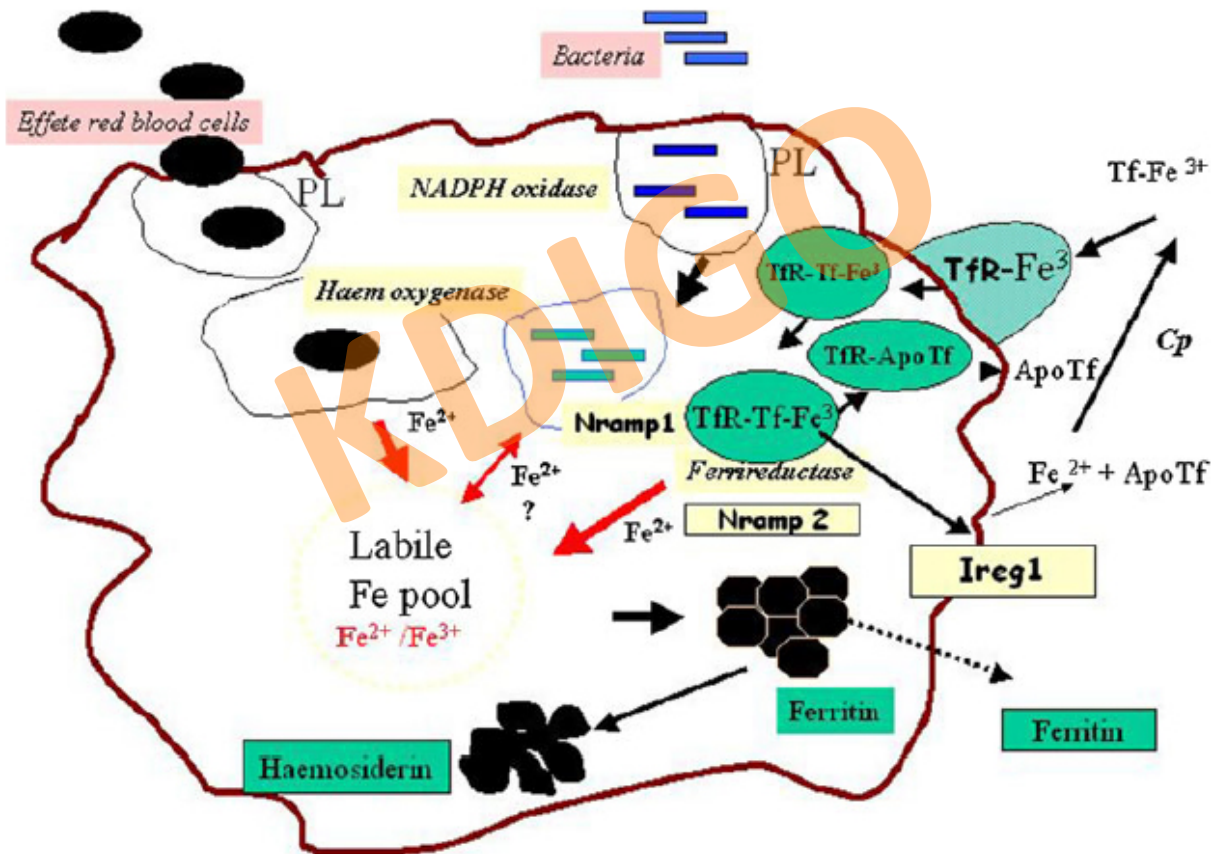


MONOCYTE/MACROPHAGE A KEY ROLE IN IRON METABOLISM AND INFLAMMATION

Innere Medizin IV
Nephrologie und Hypertensiologie

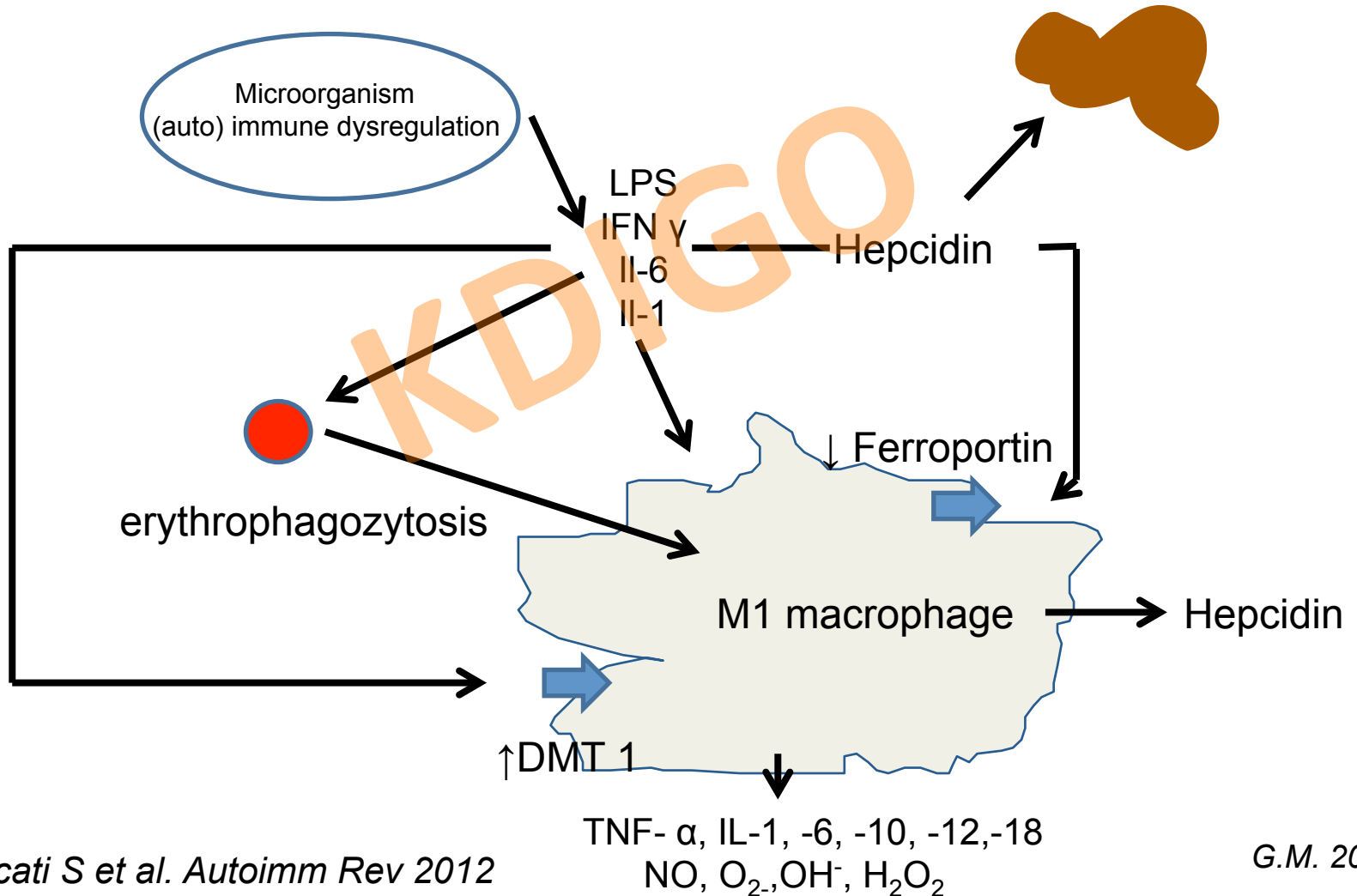


MEDIZINISCHE UNIVERSITÄT
INNSBRUCK



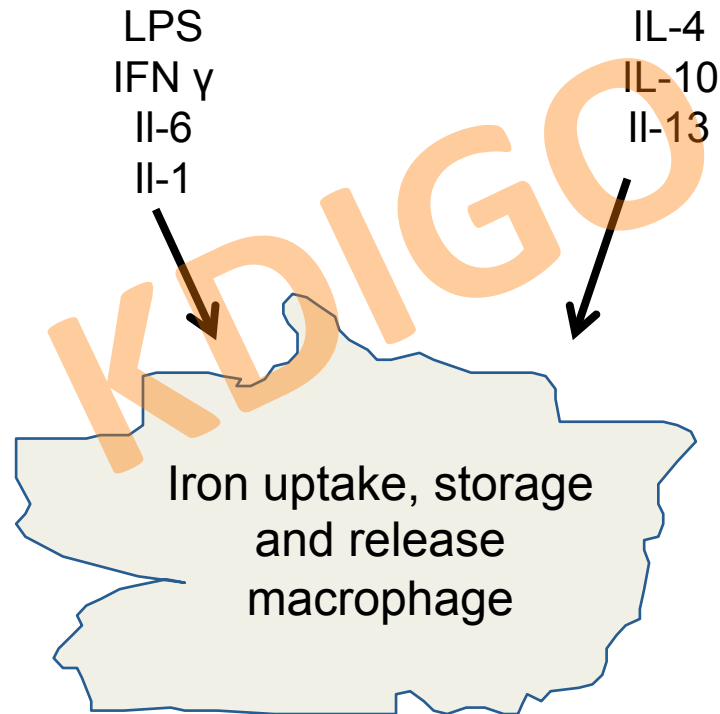


NUTRITIONAL IMMUNITY (I)





NUTRITIONAL IMMUNITY (II)





Anemia of chronic disease (ACD)

- most frequent anaemia among hospitalised patients
 - mild to moderate, normochromic, normocytic
- develops in patients with cellular immune activation
- degree of anaemia correlated to immune activation



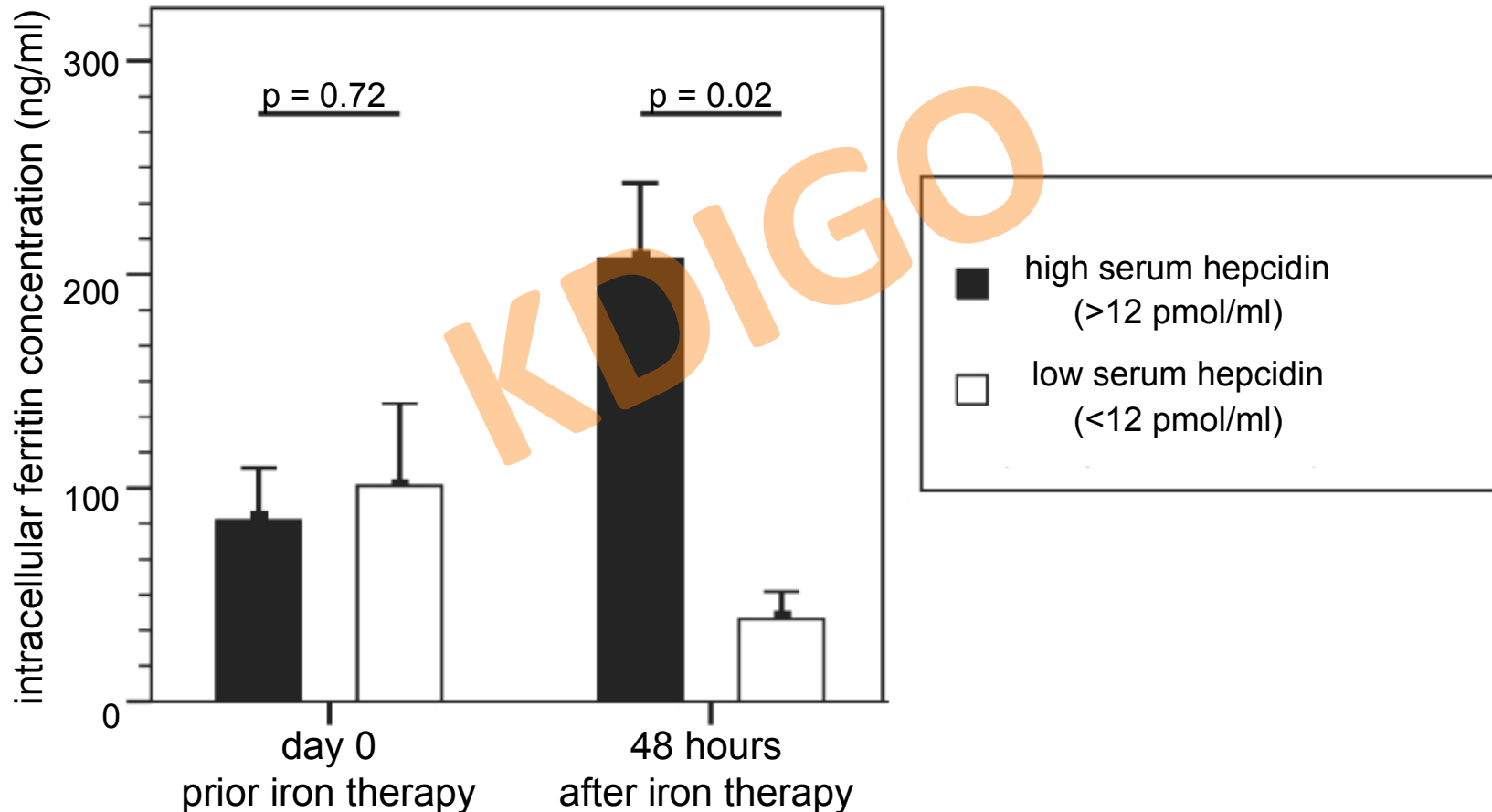
INTERACTION BETWEEN INFECTION / INFLAMMATION AND IRON METABOLISM

EFFECTS OF IRON SUPPLEMENTATION DURING INFECTION / INFLAMMATION

EFFECTS OF IRON SUPPLEMENTATION ON THE IMMUNE SYSTEM IN THE „ABSENCE“ OF INFECTION / INFLAMMATION



MONOCYTE INTRACELLULAR IRON RETENTION AFTER IV IRON IS DETERMINED BY HEPCIDIN LEVELS





An unrestrained proinflammatory M1 macrophage population induced by iron impairs wound healing in humans and mice

Sindrilaru A et al. J Clin Invest 2011

KDIGO



INTERACTION BETWEEN INFECTION / INFLAMMATION AND IRON METABOLISM

EFFECTS OF IRON SUPPLEMENTATION DURING INFECTION / INFLAMMATION

EFFECTS OF IRON SUPPLEMENTATION ON THE IMMUNE SYSTEM IN THE „ABSENCE“ OF INFECTION / INFLAMMATION



THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM



31 stable patients on hemodialysis
no clinical or routine laboratory signs of infections or inflammation

all on ESA therapy, serum ferritin 200-500 µg/l,
hemoglobin 11.5-12.5 g/dl,

one week after iron withdrawal the subjects were randomized to

Group 1: 50-150 IU/kg BW ESA / week

Group 2: 50 – 150 IU ESA/kg BW plus 100 mg iron saccharate /
week



Innere Medizin IV
Nephrologie und Hypertensiologie

THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

	baseline	3 months	p ANOVA over time	p difference in trend
Hemoglobin (g/ dl)	12.5 +/- 0.8	12.1 +/- 0.8	0.36	0.1
	12.3 +/- 0.8	12.5 +/- 1.2	0.28	
Ferritin (ng/ml)	314 +/- 129	160 +/- 97	< 0.001	< 0.001
	302 +/- 83	586 +/- 282	< 0.001	
Transferrin saturation (%)	21.5 +/- 8.6	18.4 +/- 10.2	0.31	0.08
	24.8 +/- 8.8	38.1 +/- 19.9	0.01	

iron supplementation

iron supplementation

iron supplementation

Kidney Int 2003

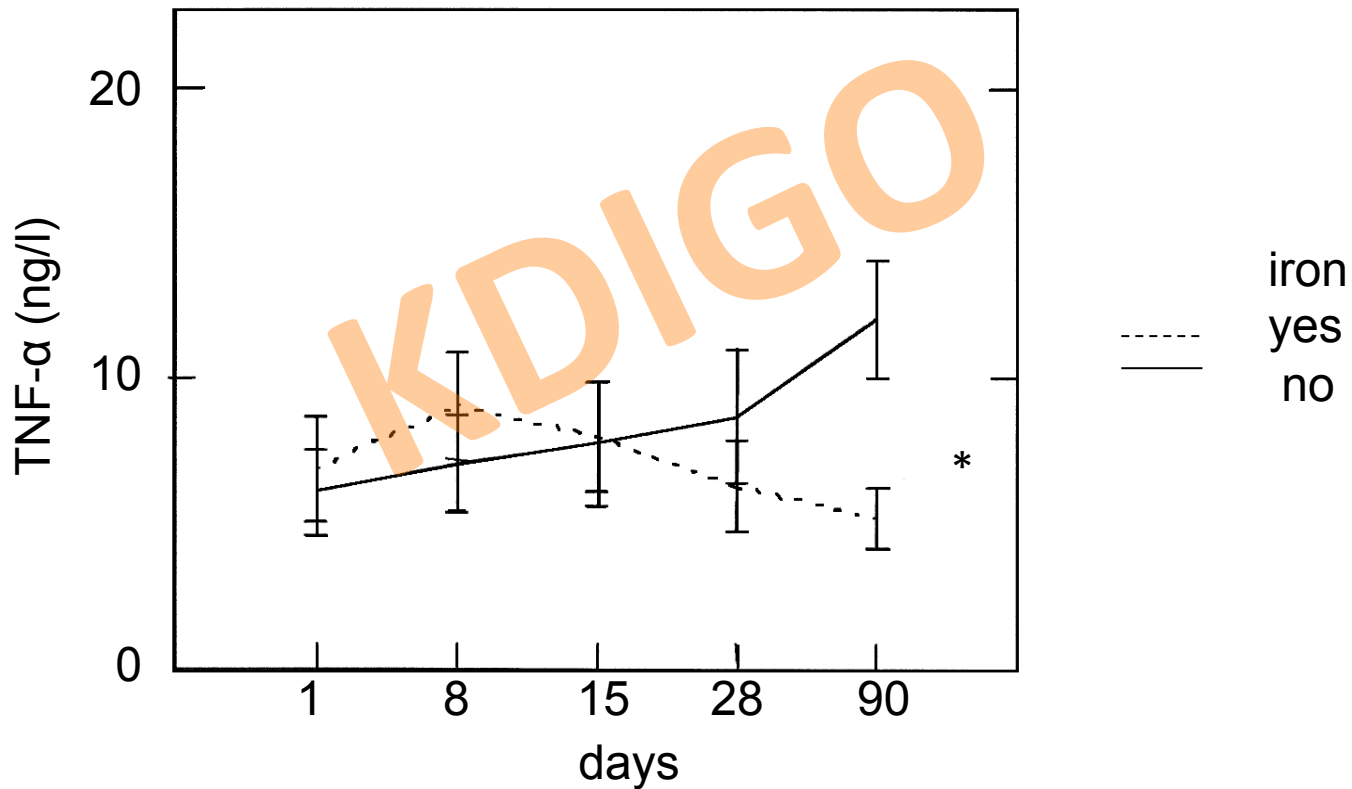
G.M. 2014



THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM



Innere Medizin IV
Nephrologie und Hypertensiologie



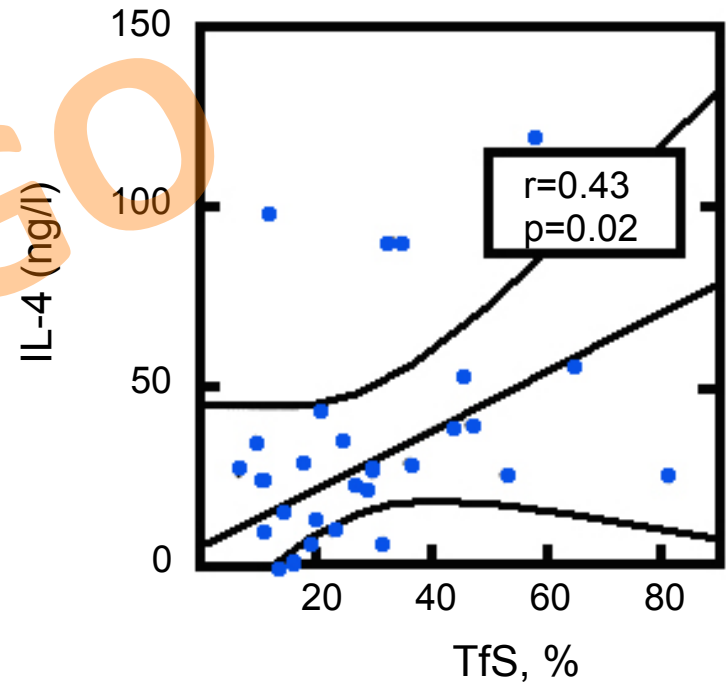
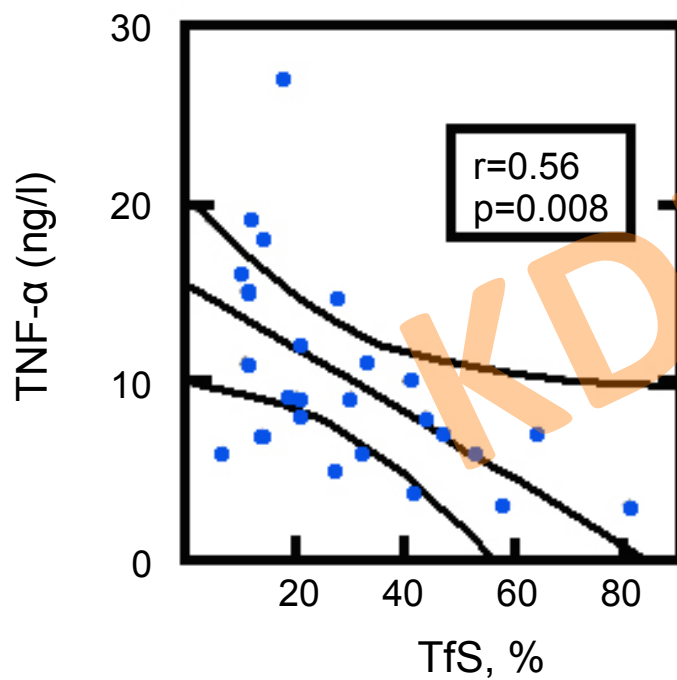
Kidney Int 2003



THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM



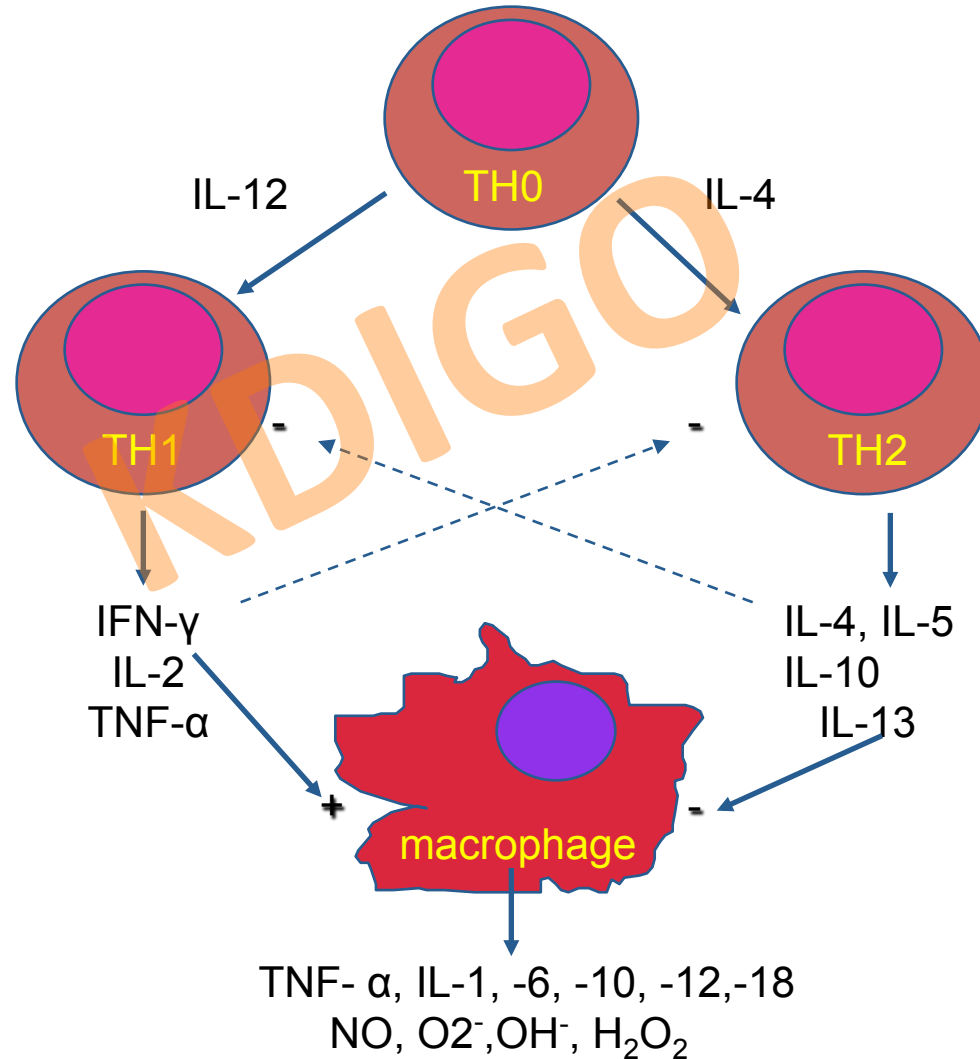
Innere Medizin IV
Nephrologie und Hypertensiologie





THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM

Innere Medizin IV
Nephrologie und Hypertensiologie



courtesy G. Weiss

G.M. 2014

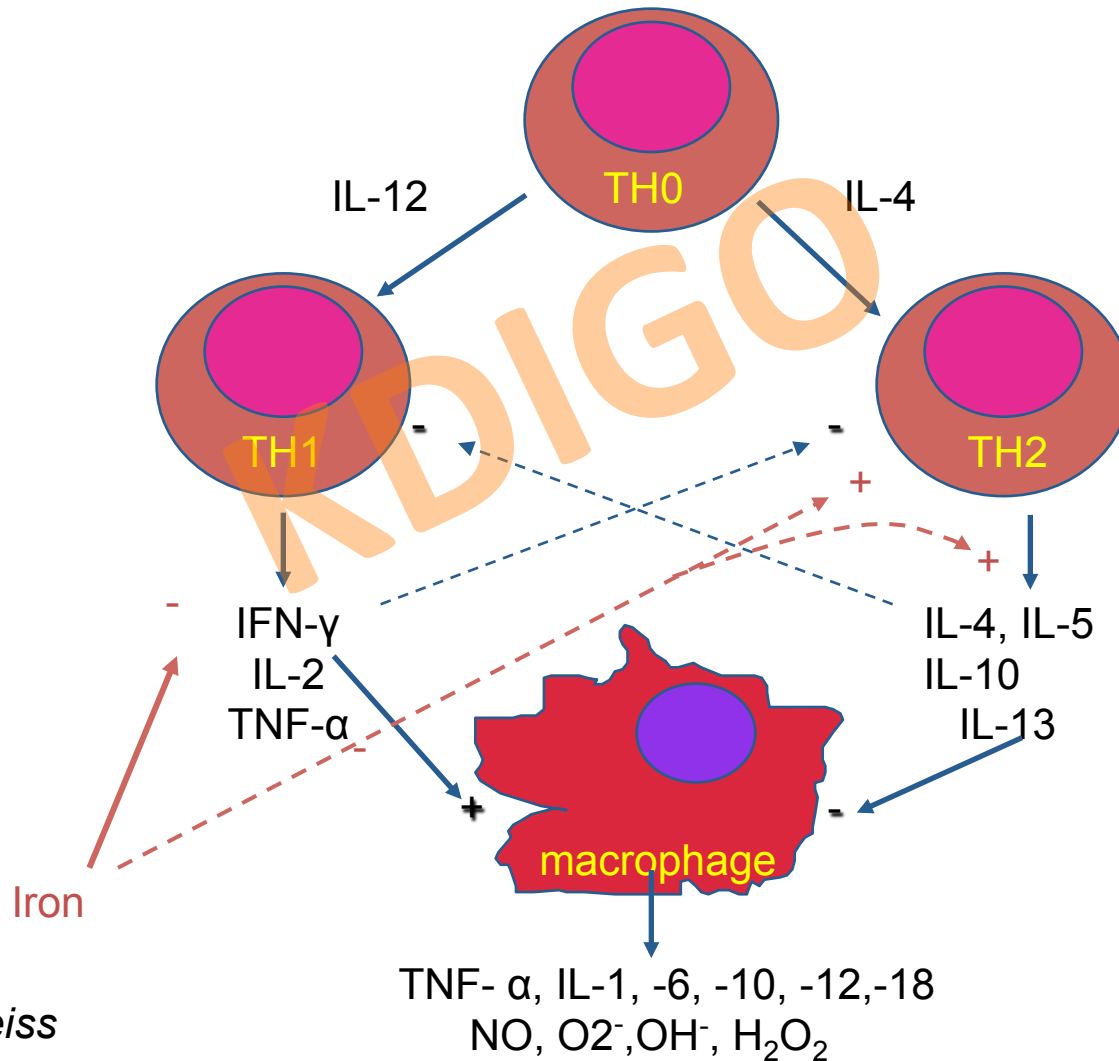


THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM

Innere Medizin IV
Nephrologie und Hypertensiologie



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK



courtesy G. Weiss

G.M. 2014

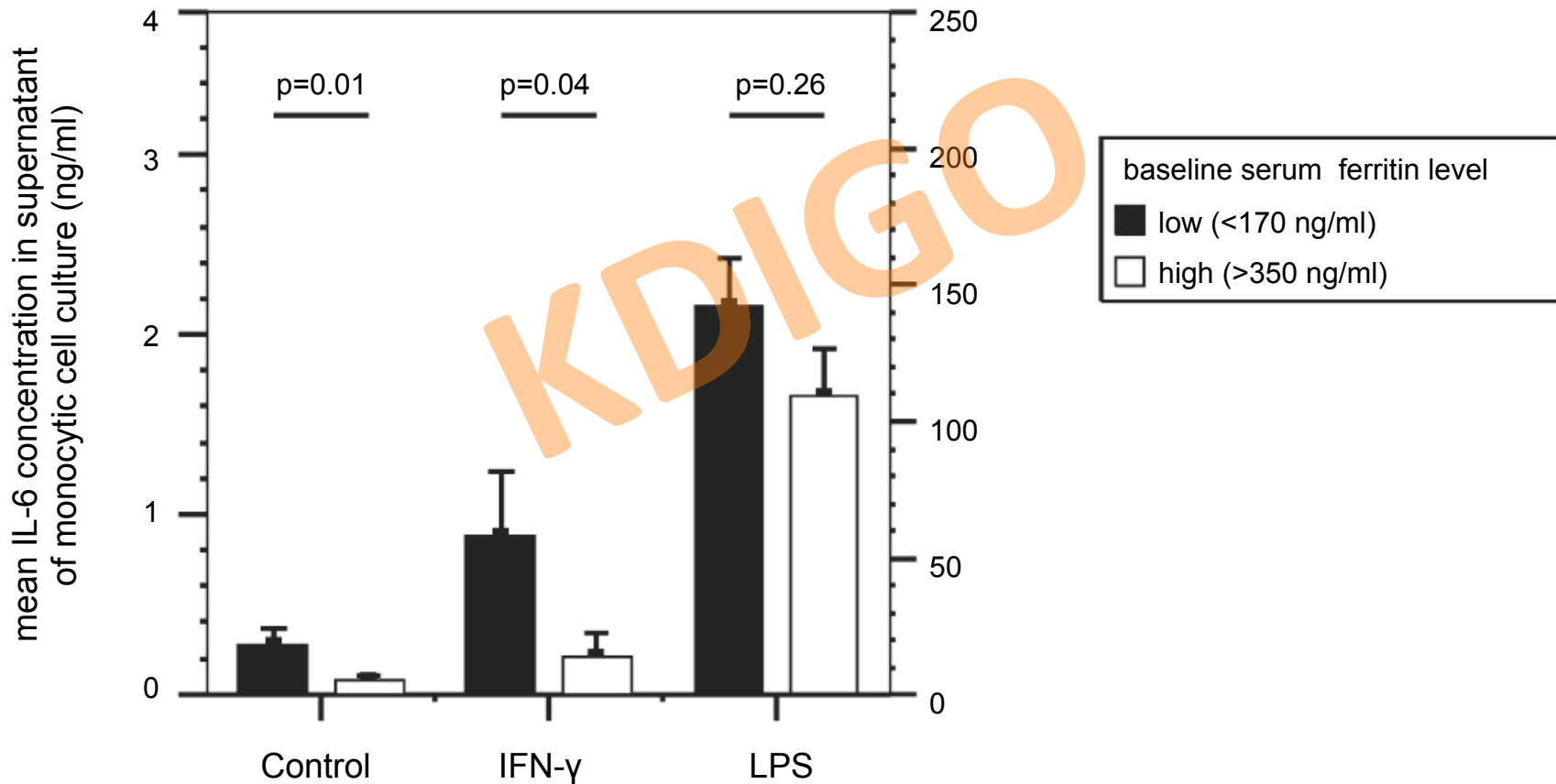


THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

Innere Medizin IV
Nephrologie und Hypertensiologie



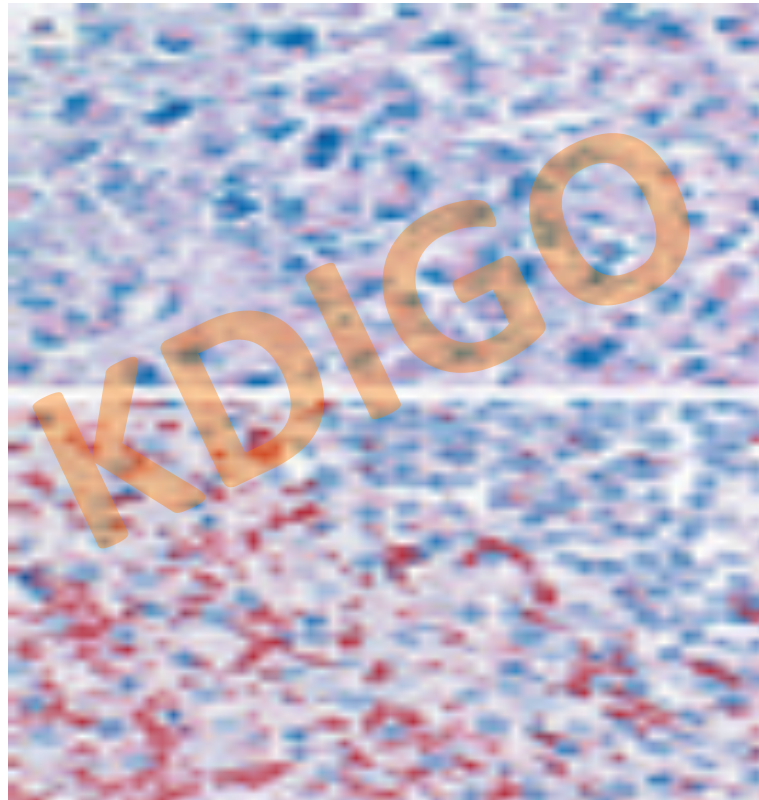


Innere Medizin IV
Nephrologie und Hypertensiologie

MAYBE NOT ONLY INCREASED IRON AVAILABILITY BUT ALSO IMPAIRED TH 1 RESPONSE ?



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

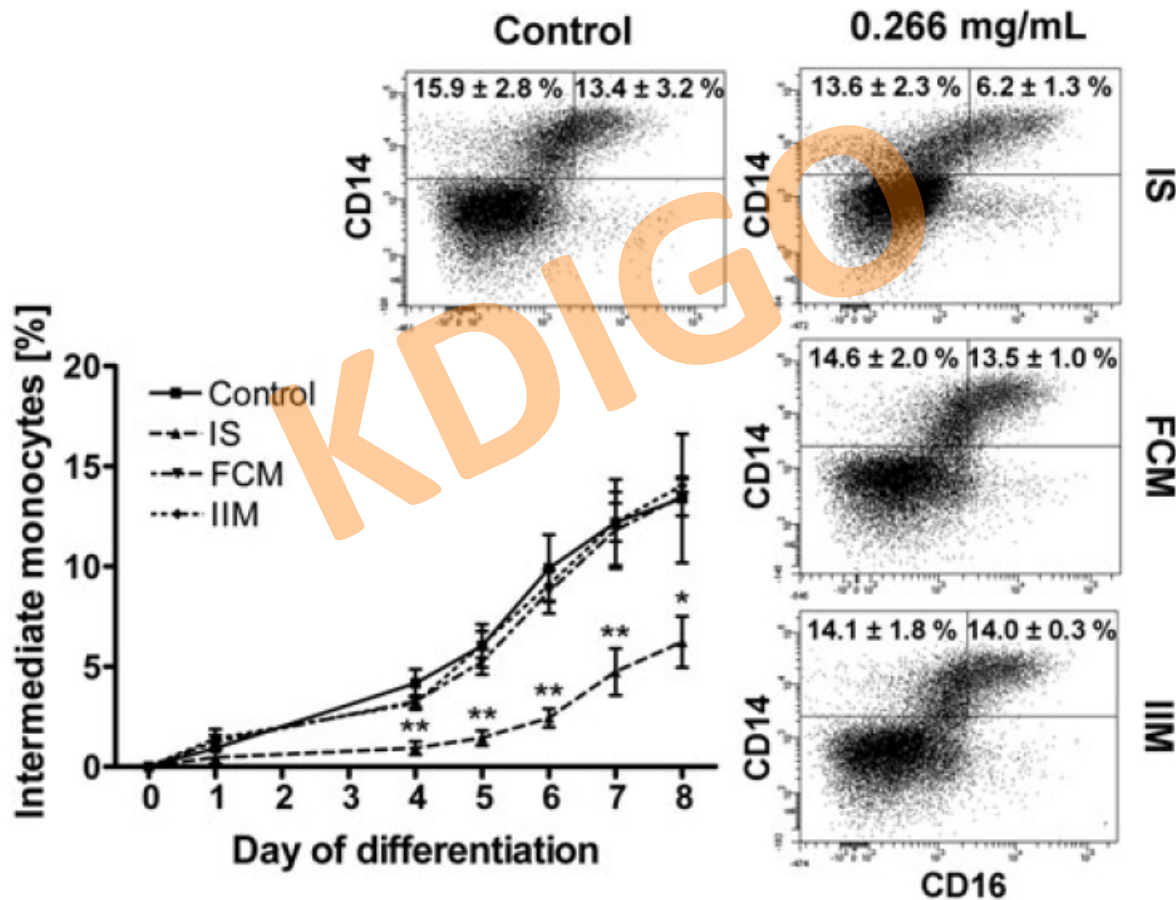


Frank KM et al. N Engl J Med 2011

G.M. 2014

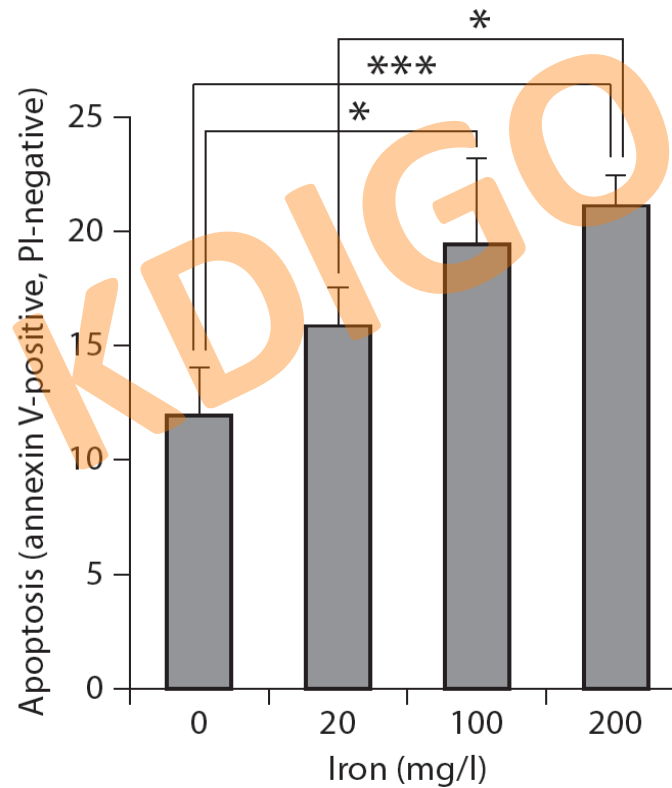


DISTINCT IMMUNOLOGIC EFFECTS OF DIFFERENT INTRAVENOUS IRON PREPARATIONS ON MONOCYTES



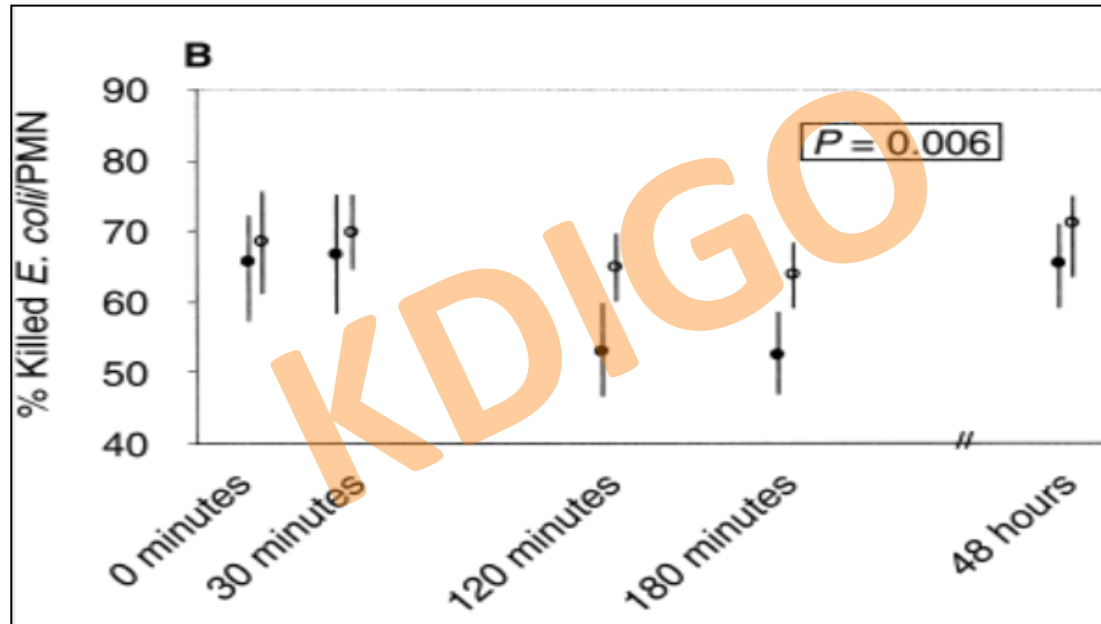


IRON SUCROSE PROMOTES APOPTOSIS IN POLYMORPHONUCLEAR LEUCOCYTES





HIGH DOSE PARENTERAL IRON SUCROSE DEPRESSES NEUTROPHIL INTRACELLULAR KILLING CAPACITY



Deicher R et al. *Kidney Int* 2003



EFFECTS OF INFECTION / INFLAMMATION ON IRON METABOLISM

EFFECTS OF IRON SUPPLEMENTATION DURING INFECTION / INFLAMMATION

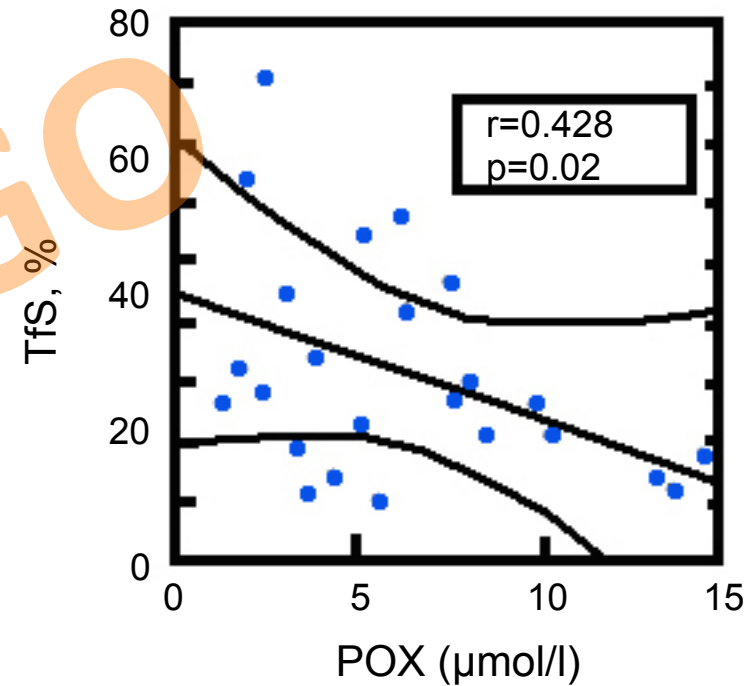
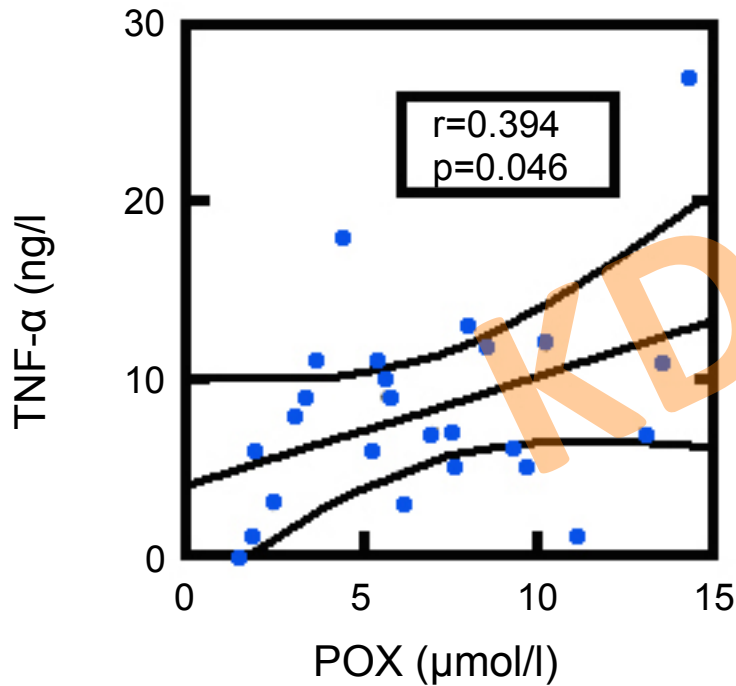
EFFECTS OF IRON SUPPLEMENTATION ON THE IMMUNE SYSTEM IN THE „ABSENCE“ OF INFECTION / INFLAMMATION



THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM



Innere Medizin IV
Nephrologie und Hypertensiologie



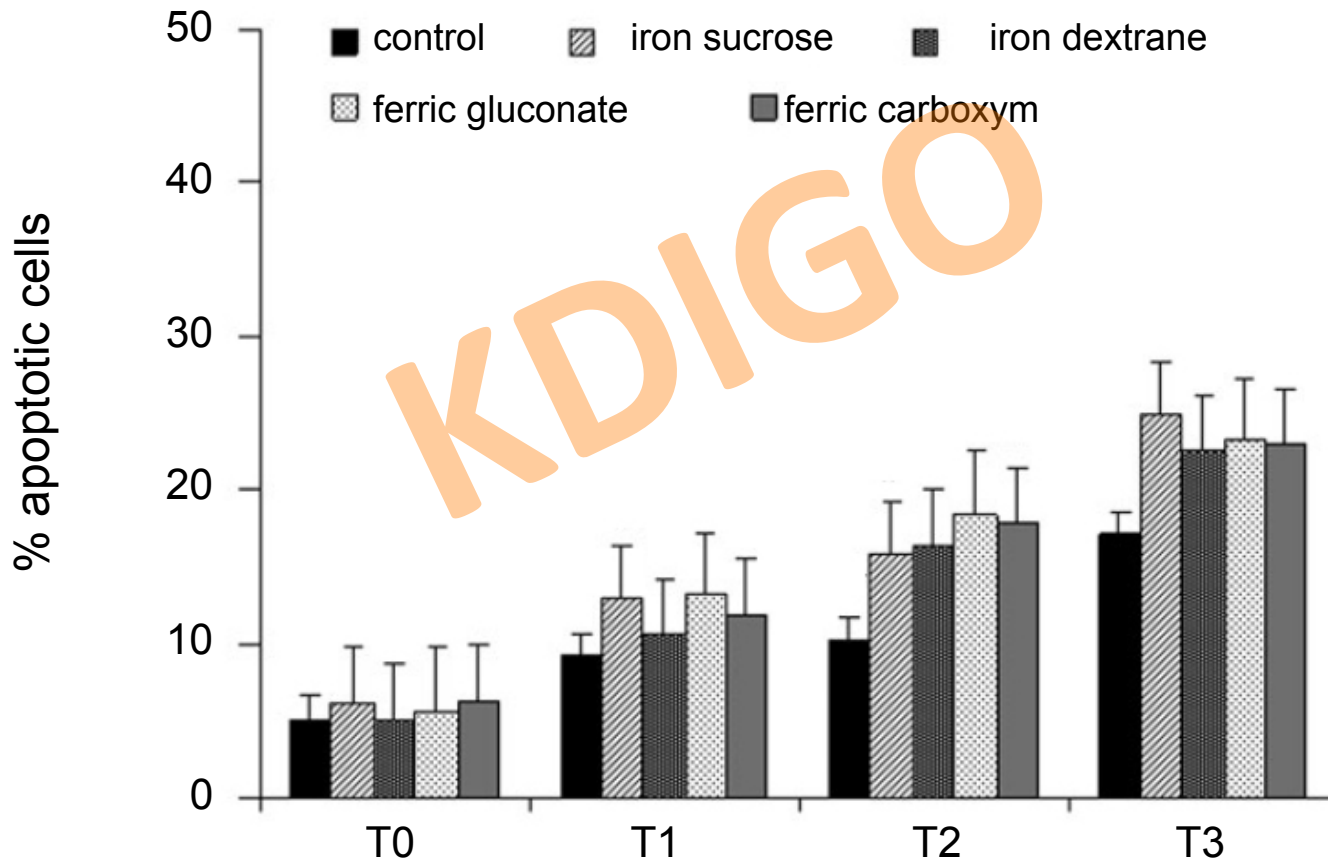


EFFECT OF DIFFERENT IRON PREPARATIONS ON APOPTOSIS OF MONONUCLEAR CELLS IN VIVO

Innere Medizin IV
Nephrologie und Hypertensiologie



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK



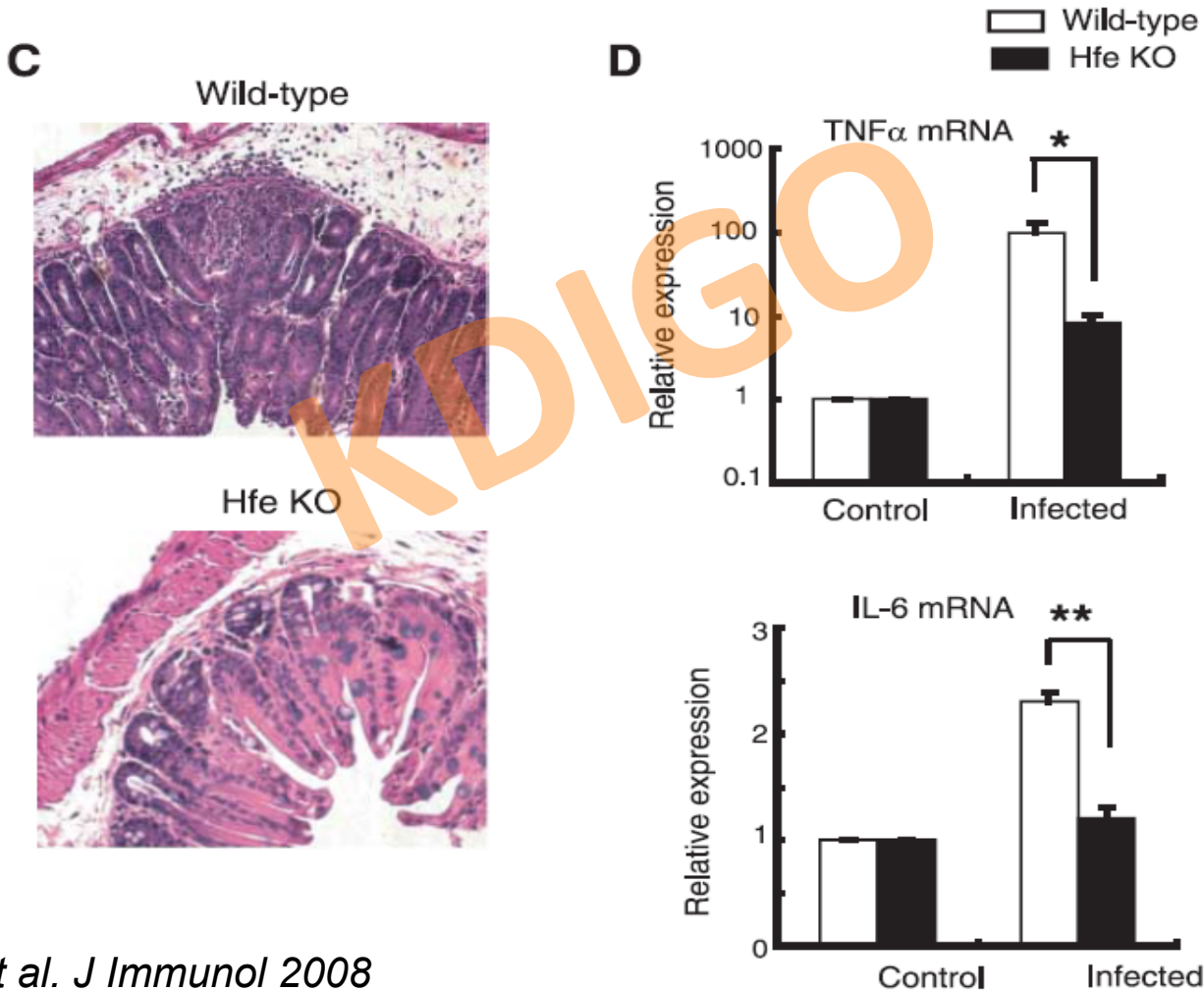


SALMONELLA INDUCED INTESTINAL INFLAMMATION IS ATTENUATED IN $Hfe^{-/-}$ MICE

Innere Medizin IV
Nephrologie und Hypertensiologie



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK



Wang L et al. *J Immunol* 2008

G.M. 2014



IRON REGULATORY PROTEINS AND IMMUNE SYSTEM

Innere Medizin IV
Nephrologie und Hypertensiologie



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

Lactoferrin	weak iron chelator	Immunoregulator effects on Th1/Th2 cell activities
Transferrin	iron transporter	present on monocytes, macrophages, T lymphocytes, required for early T cell differentiation
Transferrin receptor 1	cellular iron uptake	iron uptake by activated lymphocytes, required for DNA synthesis and cell division of T lymphocytes
Ferroportin	cellular iron exporter	toll-like gate receptor 4 mediates downregulation in infection
etc.		



IRON INHIBITS IFN γ ACTIVITY IN HUMAN MONOCYTES/MACROPHAGES

Innere Medizin IV
Nephrologie und Hypertensiologie



MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

