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

Drakesmith H et al. Science 2012
INVESTIGATION OF A RESEARCHERS DEATH DUE TO SEPTICEMIC PLAGUE BY ATTENUATED YERSINIA PESTIS

**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
- Hepcidin-mediated hepatocyte iron depletion blocks infection
- Iron stimulates, and iron chelation limits, blood-stage growth
- Malaria-induced iron redistribution promotes bacterial co-infections

*Drakesmith H et al. Science 2012*
IRON CHAPERON PROTEINS ARE ACUTE PHASE REACTION PROTEINS

Lactoferrin, Transferrin, Ferritin - chaperon proteins for iron
Haptoglobin - chaperon protein for hemoglobin
Hemopexin - chaperon protein for heme
Ward RJ et al. J Neural Transm 2011
HEPCIDIN
REGULATION BY IRON AVAILABILITY AND INFLAMMATION

MONOCYTE/MACROPHAGE
A KEY ROLE IN IRON METABOLISM AND INFLAMMATION

Ward RJ et al. J Neural Transm 2011
Microorganism (auto) immune dysregulation

LPS
IFN \( \gamma \)
II-6
II-1

Hepcidin

↑DMT 1

erythrophagozytosis

M1 macrophage

↓Ferroportin

TNF-\( \alpha \), IL-1, -6, -10, -12, -18
NO, \( O_2^-\), \( OH^-\), \( H_2O_2 \)

Recalcati S et al. Autoimm Rev 2012

KDIGO
NUTRITIONAL IMMUNITY (II)

Iron uptake, storage and release macrophage

LPS
IFN γ
IL-6
IL-1
IL-4
IL-10
IL-13
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
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MONOCYTE INTRACELLULAR IRON RETENTION AFTER IV IRON IS DETERMINED BY HEPCIDIN LEVELS

Sonnweber T et al. Nephrol Dial Transplant 2011
An unrestrained proinflammatory M1 macrophage population induced by iron impairs wound healing in humans and mice

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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

Kidney Int 2003
THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM

<table>
<thead>
<tr>
<th></th>
<th>baseline</th>
<th>3 months</th>
<th>p ANOVA over time</th>
<th>p difference in trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin (g/dl)</strong></td>
<td>12.5 +/- 0.8</td>
<td>12.1 +/- 0.8</td>
<td>0.36</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Ferritin (ng/ml)</strong></td>
<td>314 +/- 129</td>
<td>160 +/- 97</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Transferrin saturation (%)</strong></td>
<td>302 +/- 83</td>
<td>586 +/- 282</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Transferrin saturation (%)</strong></td>
<td>21.5 +/- 8.6</td>
<td>18.4 +/- 10.2</td>
<td>0.31</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>24.8 +/- 8.8</td>
<td>38.1 +/- 19.9</td>
<td>0.01</td>
<td></td>
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*Kidney Int 2003*
THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM

Kidney Int 2003
THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM

Kidney Int 2003
THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM

courtesy G. Weiss
THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM

courtesy G. Weiss

Iron

macrophage

TNF-α, IL-1, -6, -10, -12, -18
NO, O2-, OH-, H2O2

IFN-γ
IL-2
TNF-α

TH0
IL-12

TH1

TH2
IL-4
IL-4, IL-5
IL-10
IL-13
THE EFFECT OF IRON ADMINISTRATION ON THE IMMUNE SYSTEM

Sonnweber T et al. Nephrol Dial Transplant 2011
MAYBE NOT ONLY INCREASED IRON AVAILABILITY BUT ALSO IMPAIRED TH 1 RESPONSE?

DISTINCT IMMUNOLOGIC EFFECTS OF DIFFERENT INTRAVENOUS IRON PREPARATIONS ON MONOCYTES

Fell LH et al. Nephrol Dial Transplant 2014
IRON SUCROSE PROMOTES APOPTOSIS IN POLYMORPHONUCLEAR LEUCOCYTES

HIGH DOSE PARENTERAL IRON SUCROSE DEPRESSES NEUTROPHIL INTRACELLULAR KILLING CAPACITY

Deicher R et al. Kidney Int 2003
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Kidney Int 2003
EFFECT OF DIFFERENT IRON PREPARATIONS ON APOPTOSIS OF MONONUCLEAR CELLS IN VIVO

% apoptotic cells

- control
- iron sucrose
- iron dextrane
- ferric gluconate
- ferric carboxym

T0 | T1 | T2 | T3
---|---|---|---

Martin-Malo A et al Nephrol Dial Transplant 2012
SALMONELLA INDUCED INTESTINAL INFLAMMATION IS ATTENUATED IN Hfe\(^{-/-}\) MICE

<table>
<thead>
<tr>
<th>IRON REGULATORY PROTEINS AND IMMUNE SYSTEM</th>
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<tr>
<td>Lactoferrin: weak iron chelator</td>
</tr>
<tr>
<td>Transferrin: iron transporter</td>
</tr>
<tr>
<td>Transferrin receptor 1: cellular iron uptake</td>
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<tr>
<td>Ferroportin: cellular iron exporter</td>
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<tr>
<td>etc.</td>
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</table>

Ward RJ et al. J Neural Transm 2011
IRON INHIBITS IFN-γ ACTIVITY IN HUMAN MONOCYTES/MACROPHAGES