Iron and infectious disease

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IRON IS INDISPENSABLE FOR HOST AND INFECTIOUS AGENT ALIKE

Iron plays a major role in infection, being necessary in the human body to ensure proper function of the immune system, as well as in most micro-organisms for which it is an essential micronutrient for their multiplication and expression of virulence.

Role of iron in the immune response

Iron is involved at all levels of modulation of the immune system. It modulates T CD4+ lymphocytes, both T helper (Th) type 1 cells that activate macrophage microbicidal activity and Th2 cells that inhibit it. It is involved in cell-mediated responses to infection through its action in phagocytosis via the Toll-like receptor (TLR) on macrophages and neutrophils, and it is involved in the proliferation of T lymphocytes, especially CD8+ cells. Finally, it helps modulate humoral responses (interferon \( \gamma \), interleukins 2 and 6 and tumour necrosis factor \( \beta \)).

The role of iron in immunity is illustrated by the results of a study conducted in children that showed that viral and bacterial infection induces highly significant changes in the ferritin/iron ratio and serum iron concentration — in parallel to the inflammation demonstrated by a rise in C-reactive protein (CRP).

Iron requirements of infectious agents

Iron is an indispensable nutrient for bacteria. Microbiologists know that culture media must contain iron (usually in the form or iron citrate) to support the growth of certain bacteria.

It is necessary as both a macroelement (for structural molecules that constitute the bacterial architecture) and a cationic oligo-element. It plays a significant role in bacterial metabolism as an electron donor and is essential for a number of enzymatic reactions, notably those of superoxide dismutase, which participates in oxygen metabolism. Iron is also involved in nucleic acid synthesis in bacteria, viruses and parasites.

*Staphylococcus aureus* has been called an ‘iron thief’ because infection by a phage results in decreased iron sequestration by the bacterium and attenuation of its virulence. Elimination of the phage restores iron capture as well as the staphylococcal virulence.
A BATTLE FOR IRON

Thus there is a real battle for iron between the bacterium that is trying to capture iron for its own needs, and the host who is trying to limit theft of the iron and recover it to help defend against the infection.

Retention of iron by the host

In a healthy host, infection and inflammation trigger a pair of effectors, namely hepcidin and ferroportin, in order to deny the infectious agent access to its iron. The result is to inhibit the intestinal absorption of iron as well as its storage in the tissues through the sequestration of plasma iron by ferritin and of the iron in haemoglobin by macrophages.

In addition, infection and inflammation elicit antibodies directed against proteins that transport iron on behalf of micro-organisms.

Acquisition of iron by bacteria

Bacteria can capture iron through two different mechanisms: direct contact between the bacterium and iron source; and the synthesis and secretion of iron ‘sequestrators’, namely siderophores and haemophores.

Direct contact

Bacteria such as Yersinia, Escherichia coli and certain Shigella species can directly capture iron carried by transporters like ferritin, transferrin, lactoferrin, haem and haemoglobin.

The bacterial outer membrane carries receptors for transferrin (Tbp1 and Tbp2) and lactoferrin (Lbp1 and Lbp2) that bind ferric ion and import it across outer and cytoplasmic membranes into the bacterial cytoplasm (Figure 1.).

These receptors are specific to the host and the bacterium, and also to organ systems which condition the localisation of infections, e.g. transferrin receptors favour respiratory and intestinal localisations whereas lactoferrin receptors favour infection of plasma or the meninges.

Receptors expressed by certain parasites such as Trypanosoma cruzi can mutate to adapt to its environment.
Indirect acquisition

In addition, bacteria express siderophores that chelate iron. These are synthesised and secreted by the micro-organisms to scavenge and bring back iron from the environment as ferric ion. There are hundreds of these with genus-specific molecules such as pyoverdine in pseudomonas and yersinobactine in Yersinia. These siderophores bind iron in tissues and organs where it is at high concentration, notably the gut but also the respiratory and urogenital systems and the skin.

The siderophores are recognised by the ATP binding cassette family, a large family of transmembrane proteins that import various substances across the cytoplasmic membrane. Thus iron-laden siderophores are bound and the iron is ultimately released into the cytoplasm.

The bacterial cell membrane also carries proteins that can bind siderophores. These are specific for a given substrate, e.g. Staphylococcus has the transferrin-specific St.ABC receptor, Fhu CBD of Fe-hydroxamate, Sir ABC of Fe-staphylobactin, Isd DEF of Hb-Haem.

Regulation of sequestration systems

In bacteria, the synthesis of sequestration systems is regulated by a system called ferric uptake regulation (FUR), an inhibitory transcription factor that, when it binds to the promoters of genes involved in iron acquisition, represses their transcription when iron is abundant. Its activation induces a reduction in the amount of iron imported into the bacteria with a resultant attenuation of their virulence.

PATHOLOGICAL CONDITIONS

Iron deficiency

Iron deficiency leads to inhibition of microbicidal activity together with impaired cell-mediated immunity, neutrophil phagocytic activity and humoral immunity. Thus, iron deficiency predisposes to infection.

In addition, inflammation and infection cause a reduction in serum iron concentration, an increase in blood ferritin and a reduction in erythropoietin, all of which results in inflammatory anaemia, which acts as a defence mechanism against infection. It has been shown that dietary iron depletion can protect against infection by certain microbes.
Iron overload

**Haemochromatosis**

Haemochromatosis is associated with a high CD8+ cell count and phagocytic changes as well as effects on Th1–Th2 modulation. The resultant increased susceptibility to infection has been convincingly demonstrated, especially vis-à-vis *Yersinia enterocolitica* and pseudotuberculosis, *Listeria*, *Shigella*, *Aspergillus*, cytomegalovirus, parvovirus and hepatitis B and C.

In sera from individuals with haemochromatosis, Anne Jolivet-Gougeon and colleagues in Rennes has shown in vitro reduced defence capacities against *Salmonella typhimurium* (Figure 2.) and reduced production of antibodies against certain bacteria, notably *Yersinia enterocolitica* 03.

![Figure 2. Decrease in antibacterial effect of sera from patients with haemochromatosis](image)

Antibacterial activity in sera from different populations: control (empty blocks), patients with haemochromatosis without iron (light grey) and patients with haemochromatosis together with iron overload (dark grey).

(a) After 3.5 hours of incubation at different dilutions of serum (1:2, 1:4, 1:8 and 1:16) in the culture medium, compared with unspiked culture medium. 
(b) After 22 hours of incubation. Delta log10 = log10 CFU (spiked with serum) – log10 CFU (unspiked).

The same risk of infection can be observed in other pathologies associated with iron overload such as beta-thalassaemia, sickle cell anaemia, congenital sideroblastic anaemia, porphyria cutanea tarda and hepatitis; similarly, in patients on dialysis or who are overweight and following liver transplantation or excessive oral iron supplementation.

**Main pathogens**

The main pathogens concerned are intracellular micro-organisms such as *Yersinia*, *Salmonella*, mycobacteria and *Listeria*. Fungi such as *Aspergillus*, *Candida*, *Histoplasma* and parasites like *Plasmodium*, *Trypanosoma*, *Entamoeba* may also profit.

Nevertheless, *Yersinia* is the most common micro-organism that infects patients with iron overload. For this reason, fever in a patient with haemochromatosis ought to point to this bacterium and conversely, a positive *Yersinia* result in a blood culture should motivate testing for iron overload.

**Iron exacerbating infection**

Although it may not always be very well documented, it is known that iron overload can exacerbate a number of infectious diseases. In Africa, it has been shown to exacerbate tuberculosis. In HIV infection, iron supplementation in the management of pneumocystis pneumonia is associated with progression to AIDS. In hepatitis B, especially with intercurrent infection with delta virus, iron overload speeds up the progress towards fibrosis. The same is seen in hepatitis C, and it has been shown that the ferritin level correlates with fibrosis.
and is predictive of responsiveness to treatment. Women with high blood ferritin find it more difficult to clear oncogenic human papilloma virus-16. Mortality is increased in malaria.

**Chelating agents and infection: paradoxical dual action**

Iron-chelating agents act in two ways: one negative releasing iron and making it available for bacteria; and another positive through a bacteriostatic effect as observed with deferoxamine *(in vitro*, it inhibits *Staphylococcus, Escherichia coli, Klebsiella, Proteus, Salmonella, Pseudomonas aeruginosa, Enterobacter*, etc.). Deferoxamine acts synergistically with antibiotics and accelerates the clearance of *Plasmodium falciparum* as well as having activity against HIV. Lactoferrin, a naturally occurring chelating agent, also has bactericidal and bacteriostatic activities.

**Hepcidin and antibiotics**

Hepcidin acts synergistically with antibiotics and is an antagonist to the culture of *Staphylococcus aureus, Streptococcus pyogenes* and *Pseudomonas aeruginosa*.

**Towards a new type of vaccine?**

It has been suggested that as bacterial iron transporter proteins can elicit antibodies, it should be possible to develop vaccines against bacteria that exploit them. Experiments in mice have shown that such a vaccine against *Listeria* improves survival.

**REFERENCES** *(Underline references are linked to pub Med abstracts)*