Iron Dynamics Shape Host-Pathogen Interactions

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Abstract

Hosts and their pathogens often compete for trace metal elements that are essential to each of their survival. Iron is one of these trace metal elements and consequently, iron dynamics are central in host-pathogen interactions. Here we review how competition for iron during infection influences host-pathogen interactions and shapes disease outcomes. Hosts have developed diverse mechanisms to limit nutrient availability to the pathogen, also known as nutritional immunity. In response to infection, vertebrate, invertebrate, and plant hosts generate a hypoferremic environment using a variety of iron-binding proteins and chelators, alongside iron transporters, to limit pathogen replication. To counter nutritional immunity responses, pathogens use TonB-dependent (e.g., siderophores) and TonB-independent mechanisms to scavenge ferric and ferrous iron. Pathogens also compete with the host-associated microbiota to access iron. Competition between microbes for iron can either hinder or facilitate pathogen establishment and proliferation within hosts. Iron dynamics are an exciting new avenue for therapeutic interventions that may be employed against a broad range of pathogens.

1. Introduction

Iron is an element present ubiquitously in the environment in either of its two oxidation states: ferrous or ferric as minerals or ions in water (Pérez-Guzmán et al. 2010). It plays a vital role in biological processes, including the generation of ATP (as a cofactor of some proteins involved in the citric acid cycle and electron transport chain), DNA synthesis (as a cofactor of ribonucleotide reductase), and oxygen transport (as heme in hemoglobin) (Bogdan et al. 2016). The growth of many pathogens depends on iron, and its acquisition is fundamental for their survival in the host (Doherty 2007). The host can manipulate iron bioavailability, thus starving or limiting the growth of pathogens. However, pathogens encode various proteins, including siderophores, to scavenge iron from the host cells. However, host cells also synthesize iron-scavenging proteins like lactoferrin, calprotectin, and lipocalin-2, which maintain reduced levels of iron, making it insufficient for the growth of pathogens (Haschka et al. 2021). Understanding iron-mediated host-pathogen interaction during infection is thus an important area of investigation.

Hosts combat intracellular and extracellular pathogens using a variety of mechanisms to limit iron availability. To combat extracellular pathogens, mammalian hosts use lipocalin, calprotectin, lactoferrin, and transferrin (Nakashige et al. 2015; Zygiel and Nolan 2018; Kell et al. 2020; Sheldon et al. 2022). Mammalian hosts limit iron availability for intracellular hosts by diverting iron fluxes from pathogen-containing vacuoles to the cytoplasm (Zwilling et al. 1999; Haschka et al. 2021). Mammals can also use NRAMP1 (natural resistance-associated macrophage protein 1), ferroptosis, ferritinophagy, and regulation of nitric oxide (NO) levels (Zwilling et al. 1999; Haschka et al. 2021). Many hosts respond to infection by producing iron-binding proteins or chelators (molecules with a high affinity for ferric iron) that limit the availability of iron experienced by pathogens. Pathogens use transporter systems for scavenging iron from the host

environment to survive the battle for iron. During infections, pathogens interact with host microbiota to acquire iron via synergistic, antagonistic, or cheating mechanisms for obtaining iron from the host environment. These interactions also occur within the host microbiome for iron acquisition under normal conditions. Synergism is when microbes support the growth of each other in an iron-dependent manner, sharing iron equally. Cheating occurs when one species can benefit more than another due to iron uptake mechanisms, and antagonism occurs when one species succeeds over the other in sequestering iron. Antagonistic interaction is primarily observed in iron-limiting conditions (Ellermann and Arthur 2017; Kramer et al. 2020; Kern et al. 2021). These interactions add to the complexity of iron dynamics in the host system during co-infections, leading to an imbalance in the microbial community or dysbiosis in the host.

In this review, first, we summarize the mechanisms of host and pathogen scavenging of iron and the impacts of iron availability on the host and microbes. Then, we describe host consequences of iron-mediated interaction between resident microbiome and pathogens under normal conditions and during infections. Finally, this review highlights the recent clinical developments using iron as therapeutics to treat infections and diseases.

2. Host-Pathogen competition: Host Sequestration of Iron

2.1 Host Sequestration and Mechanisms of Iron-Dependent Nutritional Immunity. The ability of hosts to manipulate iron availability allows them to starve or otherwise limit the reproduction of pathogens. A wide range of taxa, including vertebrate and invertebrate animals and plants, use iron-binding proteins or chelators to produce a hypoferremic environment in response to infection. To create a hypoferremic environment for extracellular pathogens, hosts sequester iron using iron-binding proteins or chelators. Mammals use lipocalin to bind microbial siderophores, thereby

limiting the ability of some pathogens to steal iron from their environment (Sheldon et al. 2022). Additionally, in mammals, calprotectin chelates ferrous iron (Nakashige et al. 2015; Zygiel and Nolan 2018), whereas lactoferrin and transferrin bind ferric iron (Kell et al. 2020). Additional uptake in mammals can be facilitated by the Mononuclear-Phagocytic System (MPS), the binding of free hemoglobin by haptoglobin, and the scavenging of hemoglobin by hemopexin (Parrow et al. 2013). The fruit fly, *Drosophila melanogaster*, uses transferrin-1 to limit *Pseudomonas aeruginosa* infection (Iatsenko et al. 2020). The thale cress, *Arabidopsis thaliana*, uses *Arabidopsis thaliana* defensin type 1.1 (AtPDF1.1) to chelate apoplastic iron in response to *Pectobacterium carotovorum* infection (Hsiao et al. 2017) (Figure 1).

Iron fluxes are diverted from pathogen-containing vacuoles to the cytoplasm to create a hypoferremic environment for intracellular pathogens. Mammalian NRAMP1 is one such antiporter underlying this mechanism, and that is localized to the late endosomal/lysosomal membranes of macrophages and neutrophils (Zwilling et al. 1999; Haschka et al. 2021). However, NRAMP4 in *A. thaliana* is a homolog of mammalian NRAMP1 that generates an oxidative burst response that limits extracellular infection (Segond et al. 2009). Intracellular pathogens in mammals are further targeted through ferroptosis, ferritinophagy, and nitric oxide (NO) level regulation. In macrophages, ferroptotic stress can be transferred from the cytosol to vacuoles containing pathogens through ferroportin-mediated transport (Ma et al. 2022). Similarly, NO stimulates levels of Ferroportin 1 (FPN1)-mediated iron efflux from macrophages upon *Salmonella* infection (Lim et al. 2018; Nairz and Weiss 2020). Although the mechanisms may vary, the use of iron in nutritional immunity is conserved across taxa and is critical for mitigating infection. Therefore, the perturbation in regulating these iron-binding proteins can result in altered host outcomes.

2.2 Iron Availability Impacts Host Outcomes. Misregulation in iron homeostasis can directly affect infection outcomes. Below are a few examples of genetic backgrounds that affect iron availability and disease severity caused by various microbial pathogens. Absence of the siderophore-binding protein Lipocalin-2 (Lcn2) in Lipocalin-2 -/- mice impairs resistance to *Acinetobacter baumannii*, leading to increased bacteremia and pneumonia (Sheldon et al. 2022). Lipocalin-2 loss of this protein also results in worsened parasitemia, anemia, and blood loss during malaria parasite infection due to weakened innate and adaptive immune response activation (Zhao et al. 2012). Siderocalin, a siderophore-binding protein, protects the host during *Mycobacterium tuberculosis* infection by inhibiting its intracellular replication (Johnson et al. 2010). The iron chelator calprotectin, which is bound with neutrophils extracellular traps (NETs), defends hosts against *Candida albicans* infection. Loss of calprotectin results in a complete loss of antifungal activity in NETs (Urban et al. 2009). The loss of the chelator lactoferrin increases inflammation and susceptibility to *E. coli* due to increased microbial adhesion. These findings indicate that lactoferrin is a potential therapeutic target for gut-associated infections like inflammatory bowel disease (IBD) (Chen et al. 2011; Drago-Serrano et al. 2017). Hepcidin is a regulator of iron homeostasis. Lower levels of hepcidin result in increased *Flavobacterium columnare* and gill rot susceptibility in *Ctenopharyngodon idella* because iron export by ferroportin is not downregulated (Chen et al. 2020). A mutation in the cystic fibrosis transmembrane conductance regulator, CFTR (ΔF508), is linked to iron misregulation and potentially underlies the increased *P. aeruginosa* biofilm formation in patients carrying this mutation (Moreau-Marquis et al. 2008). The inherited blood disorder thalassemia results in iron overload (Taher and Saliba 2017) and is linked to intestinal damage and impaired intestinal barrier function, increasing the host risk of sepsis (Fang et al. 2018; Sae-khow et al. 2020). The genetic disorder hereditary hemochromatosis (HH) causes

increased absorption of dietary iron and preferential loading of iron into parenchymal cells instead of macrophages and other reticuloendothelial cells. Consequently, pathogens intracellular to macrophages cannot acquire iron (Moalem et al. 2004). However, IL-1β is dysregulated in HH hosts, resulting in increased susceptibility to acute systemic infection by *Yersinia pseudotuberculosis* due to intestinal damage (Das et al. 2022). These examples demonstrate the importance of genes and proteins related to regulating iron concentration in the context of infection.

An external cause of iron overload is iron supplementation, which can influence infection outcomes like the internal mechanisms described in the previous section. Through intravenous administration in hosts, iron supplementation increases overall infection risk by elevating available iron levels and promoting the growth of pathogens (Shah et al. 2021). Iron deficiency confers protection against malaria parasite infection by reducing parasite fitness (Kabyemela et al. 2008), which can be negated by iron supplementation (Clark et al. 2014). Therefore, iron supplementation for children in malaria-endemic regions requires careful monitoring (Gwamaka et al. 2012). Iron supplementation decreases the number of CD8+ cytotoxic T cells in the spleen in mice, resulting in a more severe infection with *Salmonella enterica* serovar Typhimurium (Hoffmann et al. 2021). These examples demonstrate that iron dysregulation and availability, regardless of the underlying cause, critically influence the infection outcomes of a wide range of pathogens.

3. Host-Pathogen competition: Pathogen Scavenging of Iron

3.1 Iron Scavenging Mechanisms. Pathogen scavenging of ferric and ferrous iron is mediated by TonB-dependent and independent transporters, respectively. As ferric iron is more available in the host environment than ferrous iron, TonB-dependent transporters (TBDTs) are major importers of

iron into bacteria. All TBDTs, including those relevant to bacterial pathogens, share many common structural, mechanical, and regulatory features. TonB-dependent uptake is often used to transport siderophore-bound iron. TBDTs rely on a complex of three cytoplasmic membrane proteins, TonB, ExbB, and ExbD (Figure 2A) (Postle 2007). In TonB-dependent siderophore uptake systems, the ferric-siderophore complex is transported from the outer membrane to the periplasm by the TBDT (Krewulak and Vogel 2008). In the periplasm, the periplasmic binding protein (PBP) binds the ferric-siderophore complex, and the resulting complex is transported into the cytoplasm through an inner membrane ATP-binding cassette (ABC) (Figure 2A). The expression of all TBDTs used for ferric iron uptake is regulated by the Ferric Uptake Repressor (Fur) (Noinaj et al. 2010). When intracellular ferrous iron is in excess, Fur binds to sites on DNA encoding TonB and other iron uptake proteins, repressing their expression (Bagg and Neilands 1987). However, when intracellular ferrous iron is unavailable, Fur is unable to bind to these DNA sequences, and the TBDT system is expressed, allowing for the transport of ferric iron into the cell (Young and Postle 1994). The uptake of siderophore-bound iron through TBDTs is the major mechanism for the scavenging of ferric iron.

TonB-dependent transporters are also used to transport proteins bound to heme. Unlike the siderophore uptake system, the heme assimilation system receptor (HasR) and the *Pseudomonas* heme uptake receptor (PhuR) in the outer membrane sense and uptake heme-bound proteins in a TonB-dependent manner (Figure 2A) (Shultis et al. 2006; Celia et al. 2016). Once the heme reaches the periplasm, it binds with the PBP, as in siderophore uptake, to reach the cytoplasm (Qasem-Abdullah et al. 2017). In the cytoplasm, ferric iron is then reduced into ferrous iron via ferric iron reductase (Figure 2A). Together, TonB-dependent transport of protein-bound heme and siderophore-bound iron mediates pathogen scavenging of ferric iron.

As ferrous iron is less available in the host environment than ferric iron, TonB-independent transporters are a minor importer of iron to bacteria. One such transporter, FeoB, is responsible for the import of ferrous iron in oxidative environments with low oxygen and pH. This system is predominant in bacteria and is the only system for ferrous iron uptake. Ferrous iron is transported from the periplasm to the cytosol through the FeoB transporter (Figure 2B). The cytosolic proteins FeoA and FeoC are also implicated in ferrous iron transport, but their molecular function is unclear (Sestok et al. 2018). Thus, TonB-independent transporters, in conjunction with TBDTs, facilitate pathogen scavenging of iron in diverse host environments.

3.2 Consequences of Pathogen Iron Scavenging. The scavenging of iron through TonB-dependent and independent mechanisms imparts the ability of bacterial pathogens to replicate in the host environment and consequently cause disease. In *Pseudomonas aeruginosa* infections, the ability of the bacteria to uptake iron increased growth and reduced host survival (Minandri et al. 2016). Similarly, in *Francisella tularensis* infections, defects in siderophore-mediated ferric iron uptake and impaired ferrous iron uptake reduced virulence in mice (Ramakrishnan 2017). *Stenotrophomonas maltophilia* iron scavenging systems are linked to biofilm formation, the production of extracellular polymeric substances and extracellular enzymes, siderophores, and the induction of oxidative stress response, all of which are essential for survival in the host cell (Kalidasan et al. 2018). In *Staphylococcus aureus*, the iron-responsive surface determinant locus (Isd)-mediated heme uptake system has been implicated in staphylococcal abscess formation and the dissemination of pathogens into many host organ systems (Sheldon and Heinrichs 2015). Iron scavenging is thus a major determinant of pathogen growth and virulence in bacterial infections.

The role of iron scavenging systems in growth and virulence is also highlighted in parasitic and fungal infections. In *Leishmania* infections, the ferrous iron transporter *Leishmania I*ron *T*ransporter 1 (LIT1), a zinc-regulated transporter and iron-regulated transporter-like protein (ZIP), is necessary for the survival and replication of parasites within host macrophage phagolysosomes (Huynh et al. 2006). Similarly, *Histoplasma capsulatum* synthesizes hydroxamate siderophores and ferric reductases to scavenge iron from host-transferrin and/ or ferritin, facilitating its intracellular survival within macrophages (Newman and Smulian 2013). Taken together, pathogen scavenging of ferric and ferrous iron is a major virulence factor and a key modulator of within-host pathogen dynamics.

4. Pathogen-Resident Microbiota competition for Iron

4.1 Consequences of iron dynamics on host microbiomes. Iron metabolism and iron supplementation can alter the host-microbiome composition, causing dysbiosis, which is defined as the imbalance of the microbial community. *In-vitro* studies have shown that iron chelators can inhibit potentially pathogenic strains over other bacteria, suggesting that iron is important for pathogens to successfully compete with other commensals (Parmanand et al. 2019). The possible role of iron metabolism genes of the host on probiotic bacterial abundance and the community diversity of commensal bacteria have been studied in iron regulatory protein 2 (IRP2) knockout mice. IRP2 knockout mice harbored four *Lactobacillus* species in different relative abundances, suggesting that deletion of iron metabolism genes in the host can modulate the composition of commensals in the intestine (Buhnik-Rosenblau et al. 2012).

Gut microbial metabolites can also regulate the iron homeostasis of the host by suppressing Hypoxia-inducible factor 2-alpha (HIF-2α) gene activity, the master transcription factor for host

intestinal iron absorption, and upregulating iron storage protein ferritin expression (Das et al. 2020). Additionally, oral iron supplementation during the crucial recovery period after antibiotic treatment can alter the microbiome composition of the host. One Proteobacterium and two Bacteroidetes species demonstrated preferential growth in mice with oral iron supplementation after antibiotic treatment (Cuisiniere et al. 2021). Together, these studies highlight the intricate connection between changes in iron concentration and metabolism on microbiome composition, which can potentially lead to dysbiosis in the host (Figure 3).

4.2 Consequences of iron-mediated interactions between commensal and pathogenic microorganisms. The ability of commensals in the host microbiome to restrain pathogen growth often stems from iron competition. The commensal defensive symbionts within the plant rhizosphere produce siderophores that reduce the growth of plant pathogens. Similarly, human gut *Escherichia coli* strains inhibit intestinal colonization by *S. Typhimurium* through siderophore-mediated iron competition (Kramer et al. 2020). The competition between commensal and pathogenic *Enterobacteriaceae* releases Lipocalin-2, which is a host antimicrobial protein that sequesters iron. To counter this, *E. coli Nissle* more effectively scavenges iron than *S.* Typhimurium and competes with *S.* Typhimurium for the uptake of Salmochelin, thus acting in favor of the host (Deriu et al. 2013; Bäumler and Sperandio 2016). Contrary to this, *Acinetobacter baumannii,* responsible for hospital-associated bacterial diseases, colonizes and spreads among patients by inhibiting the growth of many skin and upper respiratory commensal bacteria and outcompetes these endogenous commensals through iron competition (Knauf et al. 2022). A study that explored siderophore production and virulence effect due to pathogen exploitation by commensal found that commensal *Enterococcus faecalis* exploitation of siderophores produced by

Staphylococcus. aureus leads to reduced siderophore production causing reduced *S. aureus* virulence (Ford et al. 2016). Cheating occurs when non-producers of siderophores have matching receptors for uptake and exploit the common pool of siderophores without contributing to it (Kramer et al. 2020). Understanding the interactions of complex iron-dependent commensal and pathogenic microbes and exploring commensal iron uptake mechanisms at the expense of pathogens can improve therapeutic approaches to many diseases (Figure 3).

4.3 Consequences of iron-mediated interactions between co-infecting pathogens. Microbial co-infections can lead to iron-mediated synergistic or antagonistic outcomes impacting disease progression and inhibition of co-pathogens (Kiedrowski and Bomberger 2018). Viral infections may lead to dysregulation of host nutritional immunity leading to opportunistic secondary infections. The release of antiviral interferon-β and interferon-$\boldsymbol{\lambda}$ signals during Respiratory Syncytial Virus (RSV) infections. This increase in host interferon signaling induces host nutritional immunity dysregulation by the release of host extracellular vesicles with iron-bound host transferrin (Hendricks et al. 2016, 2021). This response to RSV infection induces biofilm formation of *Pseudomonas aeruginosa* (Hendricks et al. 2016). The increased biofilm formation may contribute to accelerated disease progression and virulence and may be particularly problematic in patients with chronic lung diseases, such as cystic fibrosis (CF) and chronic obstructive pulmonary disease. This interaction is not present for all opportunistic bacterial pathogens, as biofilm formation of *S. aureus is not impacted* by RSV co-infection (Kiedrowski et al. 2018). This is not exclusive to RSV infections; Influenza A infection downregulates lipocalin-2 via the suppression of host interleukin-1β. Lipocalin-2 is a host antimicrobial protein that sequesters iron and nutritional immunity conferred by lipocalin-2 is required to fight *S. aureus* infection (Robinson et al. 2013, 2014). Suppression of host lipocalin-2 signaling by Influenza A

causes increased bacterial load and host mortality during co-infection with *S. aureus* (Kudva et al. 2011). Viral-bacterial co-infections are demonstrated to synergistically increase virulence and disease progression of the bacterial co-pathogen.

Iron dynamics during co-infection can also interfere with the proliferation of the co-infecting pathogens. Specifically, the co-inhabitation of *P. aeruginosa* and *Aspergillus fumigatus* in a CF lung model provides interesting examples of the production and release of siderophores by opportunistic pathogens exhibiting strong antimicrobial properties. For example, pyoverdine, a siderophore produced by *P. aeruginosa*, exhibits strong antifungal inhibition to *A. fumigatus* biofilms by iron chelation and sequestration (Sass et al. 2018). In addition, *A. fumigatus* produces hydroxamate siderophores to counteract the inhibitory effects of pyoverdine (Sass et al. 2019). Understanding the dynamics of iron chelation and sequestration by two pathogens within host systems will allow for a better understanding of inter- and intra-kingdom co-infections with a special focus on individuals with chronic lung diseases (Figure 3).

5. Conclusions and Outlook

Iron is a key modulator of host-pathogen dynamics. Numerous studies have shown that the availability of iron can influence the ability of hosts to resist infections and pathogens to cause disease, as well as alter microbe-microbe interactions. Vertebrate, invertebrate, and plant hosts have evolved mechanisms to limit the availability of iron in response to infection. Inversely, many studies have demonstrated that perturbation of these mechanisms due to genetic disorders or through iron supplementation can worsen disease severity. Iron scavenging mechanisms from host environments are comparatively conserved in pathogens. Pathogens scavenge ferric iron through TonB-dependent transporters and ferrous iron through TonB-independent mechanisms.

Regardless of the mechanism, the uptake of ferric and ferrous iron enables pathogens to replicate and cause disease. Co-infection has also been shown to alter iron dynamics and host immunity while contributing to disease progression through competition, synergism, and cheating. Iron-dependent microbial interactions are therefore important considerations for disease control. Overall, the ability of the host to sequester iron, the ability of pathogens to scavenge iron, and microbe-microbe competition mediate disease dynamics and outcomes.

The current understanding of iron-mediated host-microbe interactions supports further study on this topic. Iron-mediated interactions between pathogens are an interesting opportunity for novel therapeutics. However, current therapies utilizing this mechanism are still lacking. Many current therapies involve an indirect mechanism, such as binding to pathogen-synthesized siderophores to block the binding of iron in the case of Gallium (III) (Vinuesa and McConnell 2021) or binding to siderophores to deliver antibiotics within the cell using the "Trojan horse" strategy in the case of sideromycins (Tonziello et al. 2019; Wang et al. 2022). Additionally, many iron chelators and sequestration compounds show antibiotic properties *in vitro*, but few studies have shown this *in vivo* (Ganley et al. 2020; Vinuesa and McConnell 2021). Host transferrin, an iron sequestration protein, has shown efficacy in a wide array of microbes *in vitro* and prevents the proliferation of rifampin-resistant *S. aureus in vivo* when treated with rifampin (Lin et al. 2014). The opportunity for the use of novel iron-mediated antimicrobial compounds requires further research using an *in vivo* model to better understand the potential of these mechanisms and their impact on host fitness.

Iron supplementation is a common treatment during anemia, but recent studies show potential deleterious impacts on the gut microbiome (Constante et al. 2017) and slower recovery from antibiotic therapy (Cuisiniere et al. 2021). One study has shown iron supplementation has

caused an increase in bacterial load during blood infection which can be lowered after iron starvation (Barry and Reeve 1977). Further research into oral iron supplementation treatment is warranted to determine the efficacy of this treatment during anemia.

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7. Figure Legends

Figure 1: Host sequestration mechanisms of Iron-Dependent Nutritional Immunity

Siderophore-binding proteins are well-documented in mammals and have been demonstrated to limit the iron uptake of both intracellular and extracellular pathogens (e.g., lipocalin 2 in *Acinetobacter baumannii* infections). Additionally, chelators (e.g. lactoferrin and calprotectin), present in invertebrates, vertebrates, and plants, sequester iron away from extracellular pathogens. Similarly, iron-binding proteins bind to extracellular iron and facilitate cellular uptake to prevent iron uptake from extracellular pathogens in mammals and invertebrates (e.g., transferrin-1 in *D. melanogaster* during *P. aeruginosa* infection). Natural Resistance-Associated Macrophage Proteins (NRAMPs) direct the flow of iron and have been observed to limit the growth of intracellular pathogens in mammals (NRAMP1) and extracellular pathogens in plants (NRAMP4). Ferroptosis and ferritinophagy are mechanisms by which mammalian cells can transfer oxidative stress to intracellular pathogens. Created with BioRender.com

Figure 2: TonB-dependent (ferric iron) and independent (ferrous iron) transport mechanisms

A. Ferric (Fe^{3+}, orange)-siderophore (light blue) complex and heme-binding protein (light green) are recognized by TonB-dependent receptors (FpvA, yellow), and HasR/PhuR(pink and white respectively) in siderophore and heme uptake systems respectively. TonB adaptor protein (purple) along with ExbD (green)-ExbB (blue) allow the entry of iron-bound complex into the periplasm, where it forms the complex with periplasmic binding protein (PBP). The PBP complex facilitates the entry of Fe3+-siderophore and heme complexes to enter the cytosol through ATP binding cassette (ABC), where the complex undergoes the reduction forming Fe2+ (red). **B.** TonB independent Feo-mediated ferrous iron (Fe2+) transport in bacteria, FeoB transporters(red)

transport the ferrous iron from periplasmic space to cytosol. The energy needed for this process is provided by GTP hydrolysis. All Feo transporters (FeoB (red), FeoA (pink), and FeoC (green)) are encoded in the *feo* operon; however, the role of FeoA and FeoC is still unclear.

Figure 3: Iron-dependent interactions between commensals and pathogens

Different mechanisms modulate iron homeostasis between resident microbiota, pathogen, and host. Synergism, antagonism, and cheating between commensal microbes and other pathogens can occur and affect disease progression. This disbalance is further augmented by co-infections in the host. +/- illustrates a benefit or harm to each organism. Created with BioRender.com

Figure 1

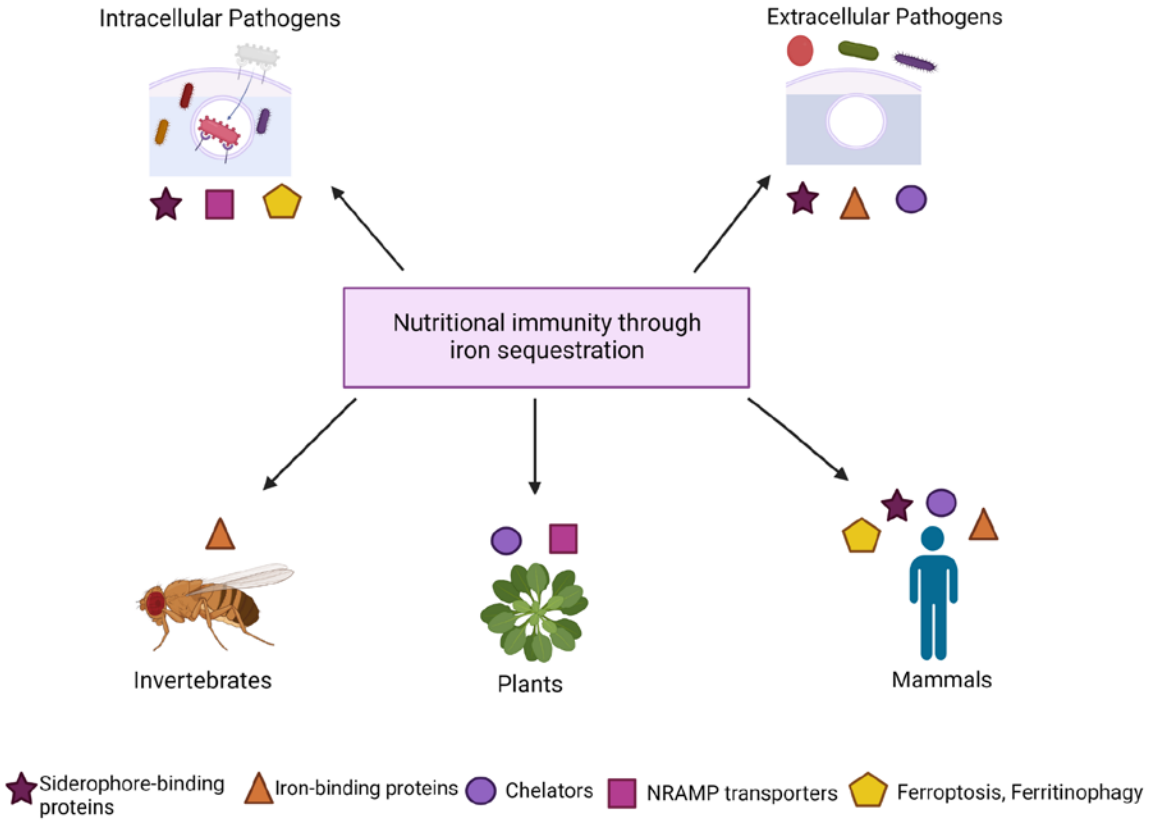

Intracellular Pathogens
Extracellular Pathogens
Nutritional immunity through iron sequestration
Invertebrates
Plants
Mammals
Siderophore-binding proteins
Iron-binding proteins
Chelators
NRAMP transporters
Ferroptosis, Ferritinophagy

Figure 2

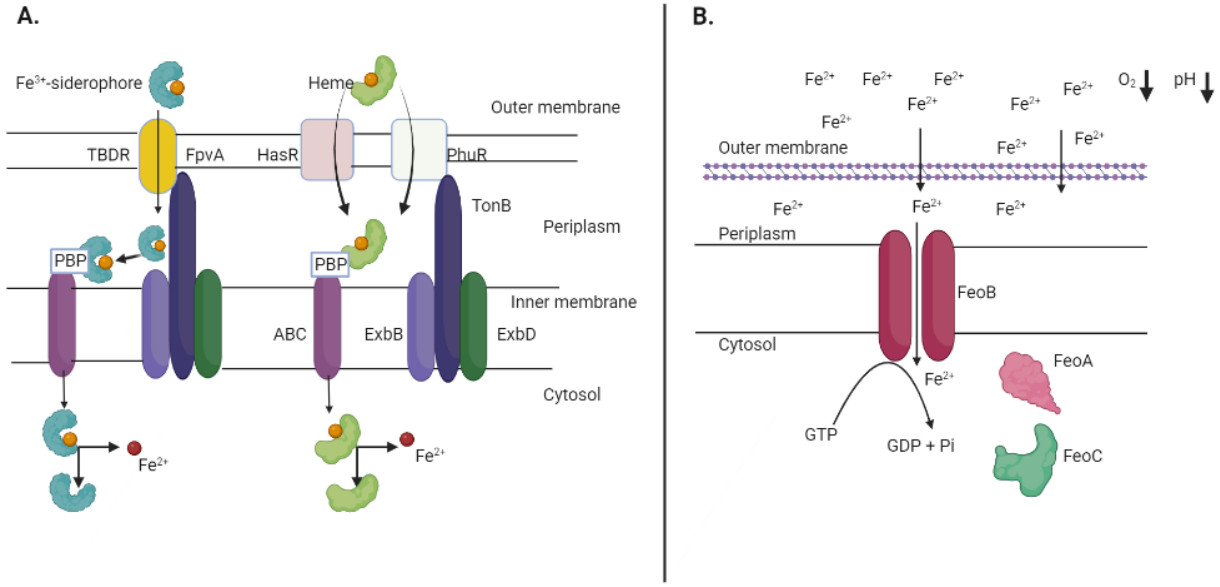
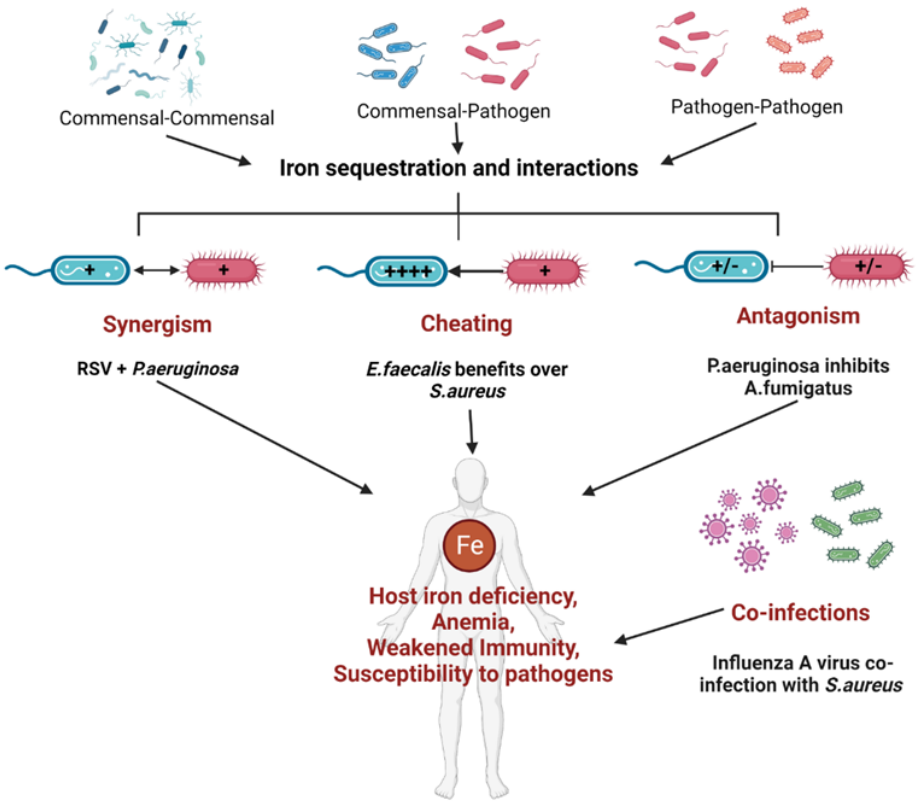

A.
Fe3+-siderophore
Heme
Outer membrane
TBDR
FpvA
HasR
PhuR
TonB
Periplasm
PBP
PBP
Inner membrane
ABC
ExbB
ExbD
Cytosol
Fe2+
Fe2+
B.
Fe2+
O2
pH
Outer membrane
Periplasm
FeoB
Cytosol
FeoA
GTP
GDP + Pi
FeoC

Figure 3


Commensal-Commensal
Commensal-Pathogen
Pathogen-Pathogen
Iron sequestration and interactions
+
+
++++
+
+/-
+/-
Synergism
RSV + P.aeruginosa
Cheating
E.faecalis benefits over S.aureus
Antagonism
P.aeruginosa inhibits A.fumigatus
Fe
Host iron deficiency,
Anemia,
Weakened Immunity,
Susceptibility to pathogens
Co-infections
Influenza A virus co-infection with S.aureus