



# Cross-Talk Between Iron and Glucose Metabolism in the Establishment of Disease Tolerance

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Infectious diseases are associated with disruption of host homeostasis. This can be triggered directly by pathogens or indirectly by host immune-driven resistance mechanisms. Disease tolerance is a defense strategy against infection that sustains host homeostasis, without exerting a direct negative impact on pathogens. The mechanisms governing disease tolerance encompass host metabolic responses that maintain vital homeostatic parameters within a range compatible with survival. Central to this defense strategy is the host's ability to sense and adapt to variations in nutrients, such as iron and glucose. Here we address how host responses regulating iron and glucose metabolism interact to establish disease tolerance and possibly modulate resistance to infection.

**Keywords:** iron metabolism, glucose metabolism, anorexia of infection, disease tolerance, nutritional immunity

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## INTRODUCTION

Avoidance, resistance, and disease tolerance are evolutionarily conserved defense strategies that limit the negative impact of pathogens on host health and fitness (1). Avoidance limits exposure to exogenous pathogens and resistance expels, neutralizes or destroys invading pathogens, while disease tolerance acts without interfering directly with pathogens (1, 2) (**Figure 1**).

Disease tolerance relies on stress and damage responses that confer tissue damage control (3), that is, support the functional output of host tissues as a means to maintain vital homeostatic parameters within a range compatible with survival to infection (2, 4, 5). Stress and damage responses sense and react to variations in environmental cues or to damage imposed to cellular macromolecules and organelles, respectively (3). These are essential to provide metabolic adaptation to the stress and damage imposed directly by pathogens or indirectly by immune driven resistance mechanisms (3, 4).

Infections can impose a distinctive host behavioral pattern referred to as sickness behavior (6, 7). This encompasses anorexia, characterized by a reduction of food intake, possibly aimed at limiting nutrient availability to invading pathogens (8, 9) (**Figure 2**). While protective against some classes of pathogens (10–12), anorexia of infection carries a high evolutionary trade-off in that nutrient deprivation can compromise host homeostasis. For example, reduced iron intake in response to infection can lead to anemia of chronic disease (13), while reduced glucose intake can lead to hypoglycemia (10, 14, 15). Here we explore how regulation of host iron and glucose metabolisms impact on the establishment of disease tolerance and possibly on resistance to infection.

## IRON METABOLISM AND DISEASE TOLERANCE

Iron is the most abundant transition metal present on Earth and perhaps for this reason was co-opted early in evolution to catalyze vital redox-based reactions in most living organisms, from prokaryotes to eukaryotes (16). Like other divalent metals, iron can shift between reduced (ferrous;  $\text{Fe}^{2+}$ ) and oxidized (ferric;  $\text{Fe}^{3+}$ ) or even higher oxidation states (ferryl;  $\text{Fe}^{4+}$ ), via reversible exchange of electrons with electrophilic or nucleophilic molecules, respectively. In doing so, iron is at the center stage of a variety of vital biological processes, including the transport and storage of gaseous molecules, energy production, as well as other components of cellular metabolism (17, 18). Probably due to its essential role in supporting these vital functions, microbial pathogens evolved multiple strategies to acquire iron from their hosts, while infected hosts co-evolved to limit iron availability to pathogens (18–22). This evolutionarily conserved defense strategy against infection is referred to as nutritional immunity (23).

### Regulation of Host Iron Metabolism in Response to Infection

Nutritional immunity is directed at inhibiting pathogens growth, via opposing mechanisms that limit nutrients' availability to intracellular or extracellular pathogens (18–22). Defense strategies limiting iron availability to intracellular pathogens rely on systemic inhibition of iron cellular import and can lead to hyperferremia (18–22). In contrast, defense strategies limiting iron availability to extracellular pathogens rely on cellular iron import mechanisms that promote cellular iron overload and hypoferremia (18–22). If uncontrolled, this can lead to the production of reactive oxygen species (ROS) via the Haber–Weiss–Fenton sequence (24), oxidizing and eventually damaging cellular macromolecules and organelles (22). In support of this notion, patients with genetic disorders characterized by cellular iron overload, such as hereditary hemochromatosis, are highly susceptible to a range of infections (25).

### Regulation of Iron Metabolism Confers Tissue Damage Control

Disruption of host iron homeostasis is a hallmark of many infectious diseases (18, 22), as illustrated for example in malaria, the disease caused by *Plasmodium* spp. infection (26–28), polymicrobial sepsis (14, 29), tuberculosis caused by *Mycobacterium tuberculosis* (30, 31) or acquired immune deficiency syndrome, caused by human immunodeficiency virus (HIV) infection (31). Regulation of host iron metabolism is critical to confer tissue damage control, and in doing so, establishes disease tolerance to infection, as demonstrated for example for malaria (32) or polymicrobial sepsis (14).

The majority of the iron present in mammals exists in the form of heme (17, 33, 34), a tetrapyrrole ring that binds a central iron atom through different nitrogen atoms (34, 35). Heme is used essentially as a prosthetic group of hemoproteins, such as hemoglobin, myoglobin, or cytochrome c, where iron is

deployed to exchange and store gaseous molecules or to transport electrons, respectively (33, 34). The largest pool of heme in mammals is found within hemoglobin in red blood cells (RBC), a prime target for invading pathogens in their search for iron (22, 33). As such, RBC lysis is a recurrent event associated with infection leading to the release of hemoglobin into plasma (17, 22, 36–38). Extracellular hemoglobin disassembles and auto-oxidizes, releasing its non-covalently bound prosthetic heme groups (33, 38) (**Figure 3**). This can lead to the generation of labile heme, that is, heme loosely bound to plasma acceptor proteins, macromolecules or low molecular weight ligands that fail to control its redox activity (36, 39). As it becomes bioavailable, a fraction of the labile heme in plasma acts in a pathogenic manner, compromising the establishment of disease tolerance to infection, as illustrated for malaria (38, 40, 41) or polymicrobial sepsis (14, 29).

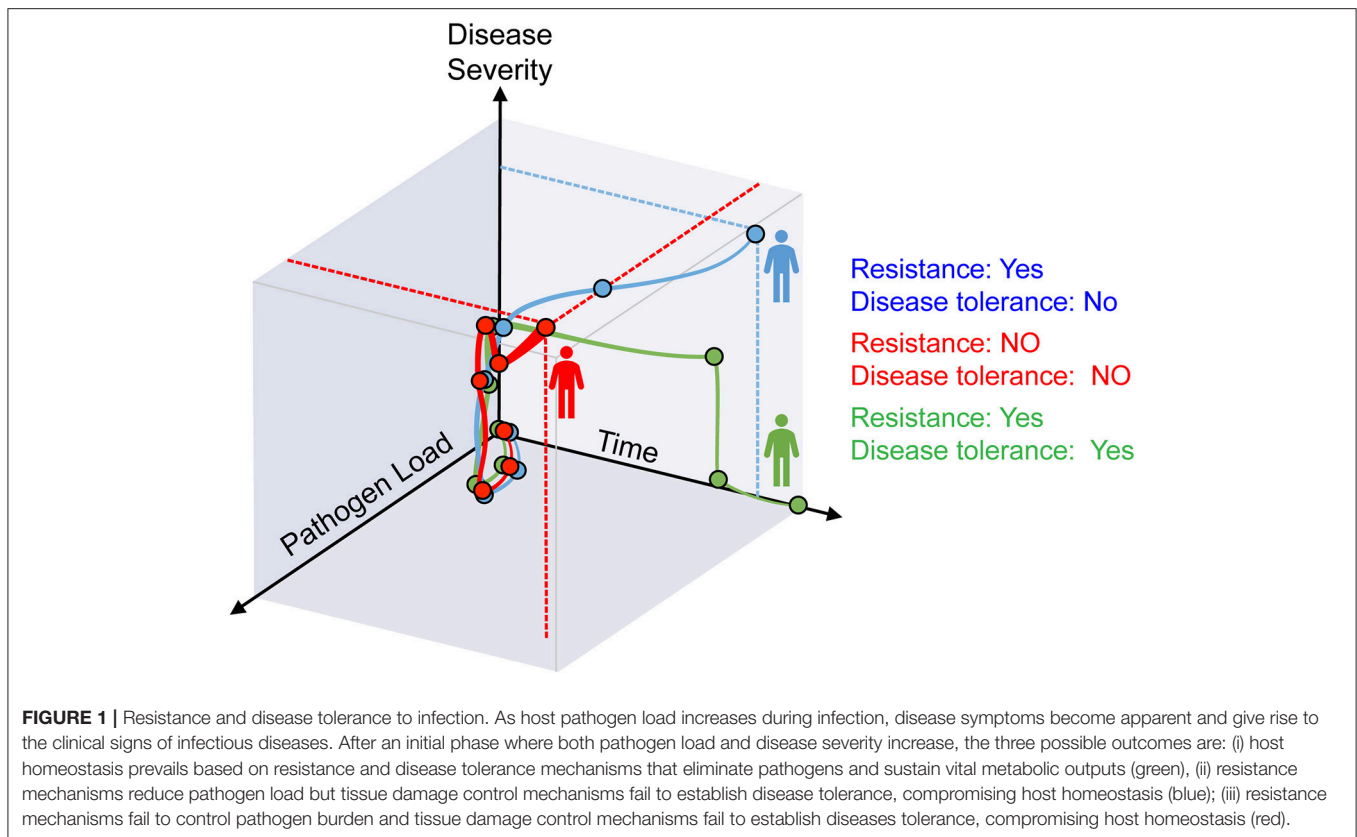
Labile heme can also compromise resistance to infection via mechanisms inhibiting macrophage phagocytosis and impairing bacterial clearance (42) or mechanisms inducing macrophages to undergo programmed cell death (43). Moreover, labile heme can also be scavenged directly by bacterial pathogens, as demonstrated in the case of *Staphylococcus aureus* (44) or *Citrobacter rodentium* (45), promoting pathogen growth and compromising host resistance to infection (21, 46).

The pathological effects of labile heme are countered by host defense mechanisms that converge at the level of heme catabolism and storage of the iron extracted from heme (33, 34, 47). Under physiological conditions heme is catabolized by heme oxygenase-1 and -2 (HO-1 and HO-2), which cleave the tetrapyrrole ring, generating equimolar amounts of iron, carbon monoxide, and biliverdin (48). Upon infection, the stress-responsive HO-1 becomes the rate limiting enzyme in heme catabolism (33), playing a critical role in the establishment of disease tolerance to systemic infections, as illustrated for malaria (40, 41, 49) or polymicrobial sepsis (29).

The iron extracted via heme catabolism by heme oxygenases, integrates the cellular labile iron pool (LIP), becoming available to pathogens while catalyzing the production of ROS via the Haber–Weiss–Fenton sequence (24) (**Figure 3**). The pro-oxidant effects associated with excess heme catabolism and LIP overload are countered via the induction of cellular iron export by the solute carrier family 40 member 1 (SLC40A1), also known as ferroportin 1 (FPN1) (17, 22). Once excreted, iron is captured in plasma by transferrin (17, 22, 50) and delivered, via the transferrin receptor, to erythropoietic precursors where iron is required to support heme and hemoglobin synthesis (17, 22).

To prevent overt accumulation of extracellular iron, ferroportin expression and activity are downregulated by hepcidin, an acute-phase 25-amino acid peptide encoded by the *HAMP* gene (51, 52). In support of this notion, hepcidin accumulates in plasma in response to infection, inhibiting ferroportin expression/activity and impairing cellular iron export (51, 52). This can lead to cellular LIP accumulation, a potentially deleterious effect countered via iron storage and neutralization by ferritin (47, 53, 54).

Ferritin is a multimeric complex composed of ferritin heavy (heart) chain (FTH) and light (liver) chain (FTL) (47, 53,



54) (**Figure 3**). The ferroxidase activity of FTH converts pro-oxidant  $\text{Fe}^{2+}$  into nucleated  $\text{Fe}^{3+}$  (47, 53, 54), preventing LIP from participating in Haber–Weiss–Fenton sequence (24), limiting ROS generation and avoiding oxidative damage (17, 33). Supporting this notion, ferritin is essential to enforce tissue damage control and to establish disease tolerance to malaria (32) and to polymicrobial sepsis (14) (**Figure 3**). This protective effect depends on the ferroxidase activity of FTH, suggesting that iron conversion to its oxidized form ( $\text{Fe}^{3+}$ ) and subsequent incorporation into ferritin, are critical to establish disease tolerance to infection.

A significant proportion of ferritin is secreted (55), suggesting that the protective effects of ferritin are not restricted to its intracellular functions. In keeping with this notion, soluble ferritin is protective against *Escherichia coli* infection (56), and acts therapeutically to establish disease tolerance to polymicrobial sepsis (14). This argues for a role of extracellular ferritin as soluble iron chelator/transporter enforcing the establishment of disease tolerance to infection. Unexpectedly, the protective effects of ferritin extends beyond its antioxidant role, in that ferritin also controls glucose metabolism (14).

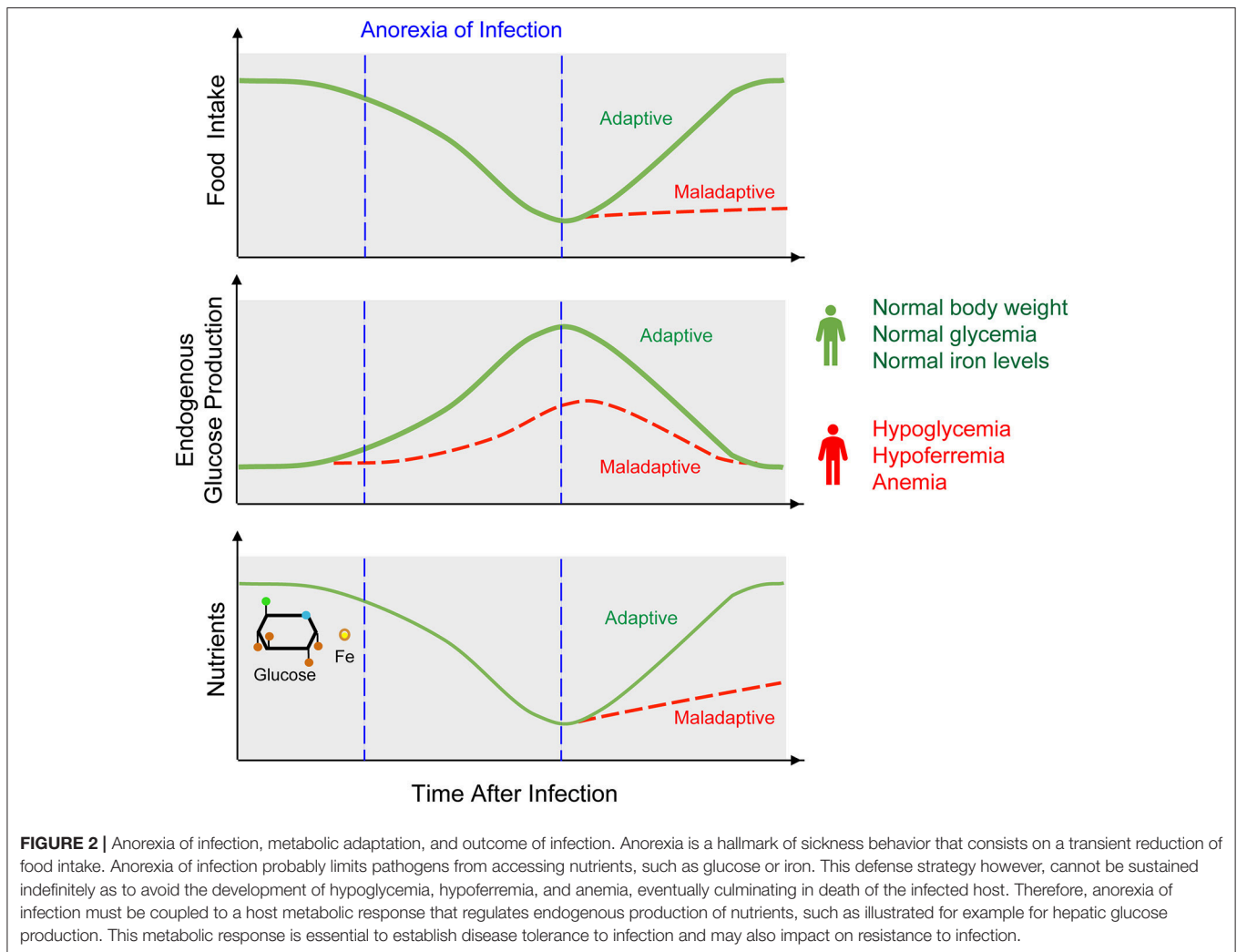
## GLUCOSE METABOLISM AND DISEASE TOLERANCE

Glucose is a key nutrient for most living organisms, acting both as a metabolic fuel for ATP production via glycolysis or mitochondrial electron transport and as a biosynthetic

intermediate for amino acid, lipid, and nucleic acid synthesis (57). While glucose intake from food allows for systemic delivery, glucose can also be synthesized endogenously from glucose precursors via gluconeogenesis or glycogenolysis in the liver, kidneys, or intestine (58). Glucose uptake from diet and its endogenous synthesis are tightly regulated to maintain blood glucose levels within a homeostatic range (5, 59). Enforcing this homeostatic range is particularly challenging during an infection (5), given that pathogens and their hosts often compete for this nutrient. Similar to iron, the infected host evolved strategies to limit glucose availability to pathogens, while maintaining glucose levels within a range compatible with survival. One of the strategies limiting glucose availability to pathogens relies on reducing glucose and glucose precursors intake from diet, via anorexia of infection. This is probably a component of nutritional immunity conferring resistance against pathogens (8–12, 60) (**Figure 2**).

## Glucose Availability in Response to Infection

The impact of anorexia of infection on the outcome of infectious diseases varies widely depending on the host and pathogen species (9–12, 61). In fruit flies, anorexia of infection promotes the establishment of disease tolerance to *Salmonella* Typhimurium infection, while compromising resistance to *Listeria monocytogenes* infection (11). In mice, anorexia of infection is protective against *L. monocytogenes* (10, 12), but deleterious against influenza virus infections (10, 62). Anorexia of



infection also impacts on the outcome of gastrointestinal parasitic infections (60, 61), reducing body weight upon *Nippostrongylus brasiliensis* infection (63), while increasing immunopathology in response to *Trichostrongylus colubriformis* infection (64).

Mechanisms regulating anorexia of infection are not clearly established (9, 10, 61), but certainly encompass pathogen sensing via host pattern recognition receptors (PRR) (9). Signaling downstream of PRR elicits the production of interleukins (IL), such as IL-1, IL-6, IL-8, or tumor necrosis factor (TNF), which signal systemically to induce anorexia of infection as well as to regulate glucose metabolism (9). One of the mechanisms via which this occurs involves the secretion of leptin by adipose tissue (9, 65), an hormone that signals in the central nervous system (CNS) to reduce food intake and regulate energy consumption (66).

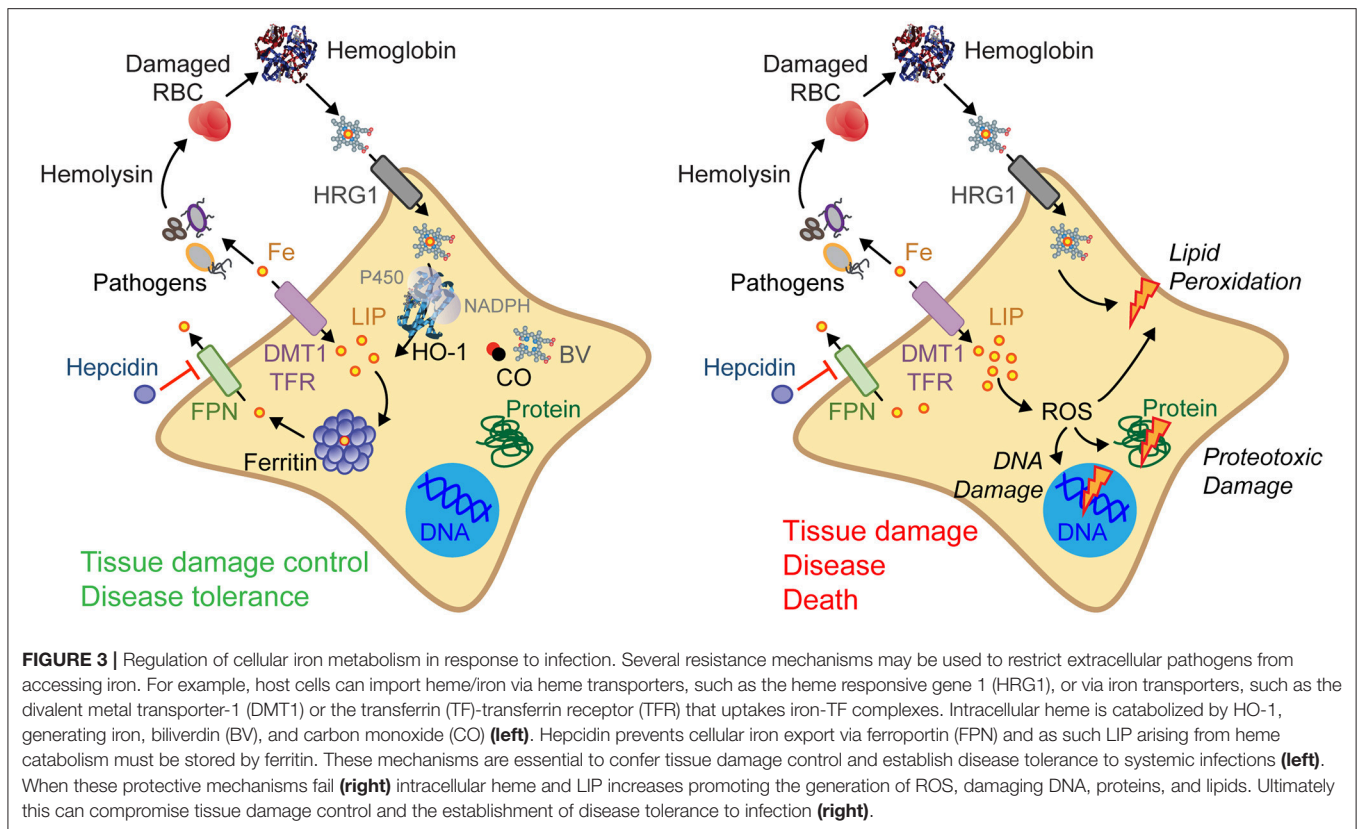
Pathogens can modulate anorexia of infection directly to promote their survival and/or transmission (9, 10, 61, 67). For example, *S. Typhimurium* inhibits PRR activation/signaling, reducing IL-1 $\beta$  secretion in the gut and increasing food consumption, as well as blood glucose levels (67). This reduces

*S. Typhimurium* virulence and promotes host disease tolerance, while increasing *Salmonella* transmission (67), most likely as an evolutionary trade-off. The nematode *N. brasiliensis* also induces anorexia, via the regulation CNS signaling (68, 69), even though the exact mechanism by which this occurs has not been established.

Anorexia of infection is also associated with reduction in caloric intake, i.e., caloric restriction, which can *per se* modulate the outcome of infection (70). For example, caloric restriction increases susceptibility to polymicrobial (71) and viral infections (10, 72), while reducing *Plasmodium* virulence and promoting survival to malaria (73).

Although protective against bacterial infections (8, 9) mechanisms reducing blood glucose levels must be tightly regulated to prevent the development of lethal hypoglycemia. In support of this notion, inhibition of hepatic glucose production in mice carrying a liver-specific deletion of glucose 6 phosphatase 1 (*g6pc1*) compromises disease tolerance to polymicrobial infections (14). This suggests that while reducing blood glucose levels can be protective against bacterial infections





(8, 9), endogenous glucose production is required to prevent the development of lethal hypoglycemia and establish disease tolerance to polymicrobial sepsis (14).

### Impact of Metabolic Diseases on Infection

The impact of glucose metabolism on the outcome of infectious diseases is illustrated by the effect of metabolic diseases, such as obesity or diabetes, on the outcome of infections. For example, hyperglycemia in diabetic rodents is associated with increased susceptibility to polymicrobial sepsis (74, 75) as well to *L. monocytogenes* (76) or *M. tuberculosis* (77) infections. Moreover, hyperglycemia promotes intestinal permeability and increases susceptibility to bacterial infection in mice (78). This pathogenic effect is mediated via glucose import by intestinal epithelial cells, disrupting the functional integrity of the gut epithelium via a mechanism that interferes with epithelial tight and adherens junctions (78). Despite this experimental evidence, whether deregulation of glucose homeostasis impacts on the outcome of bacterial infections in humans remains unclear. For example, clinical evidence suggests that diabetes mellitus is not a major risk factor for sepsis severity (79), while both hyperglycemia and hypoglycemia are major risk factors for sepsis mortality (80, 81). Of note, rodents develop hypoglycemia rather than hyperglycemia in response to bacterial infections (14, 15, 82, 83). In some cases, hypoglycemia is preceded by a transient state of hyperglycemia, but whether this is triggered by infection and/or other associated experimental procedure is not clear (14, 15).

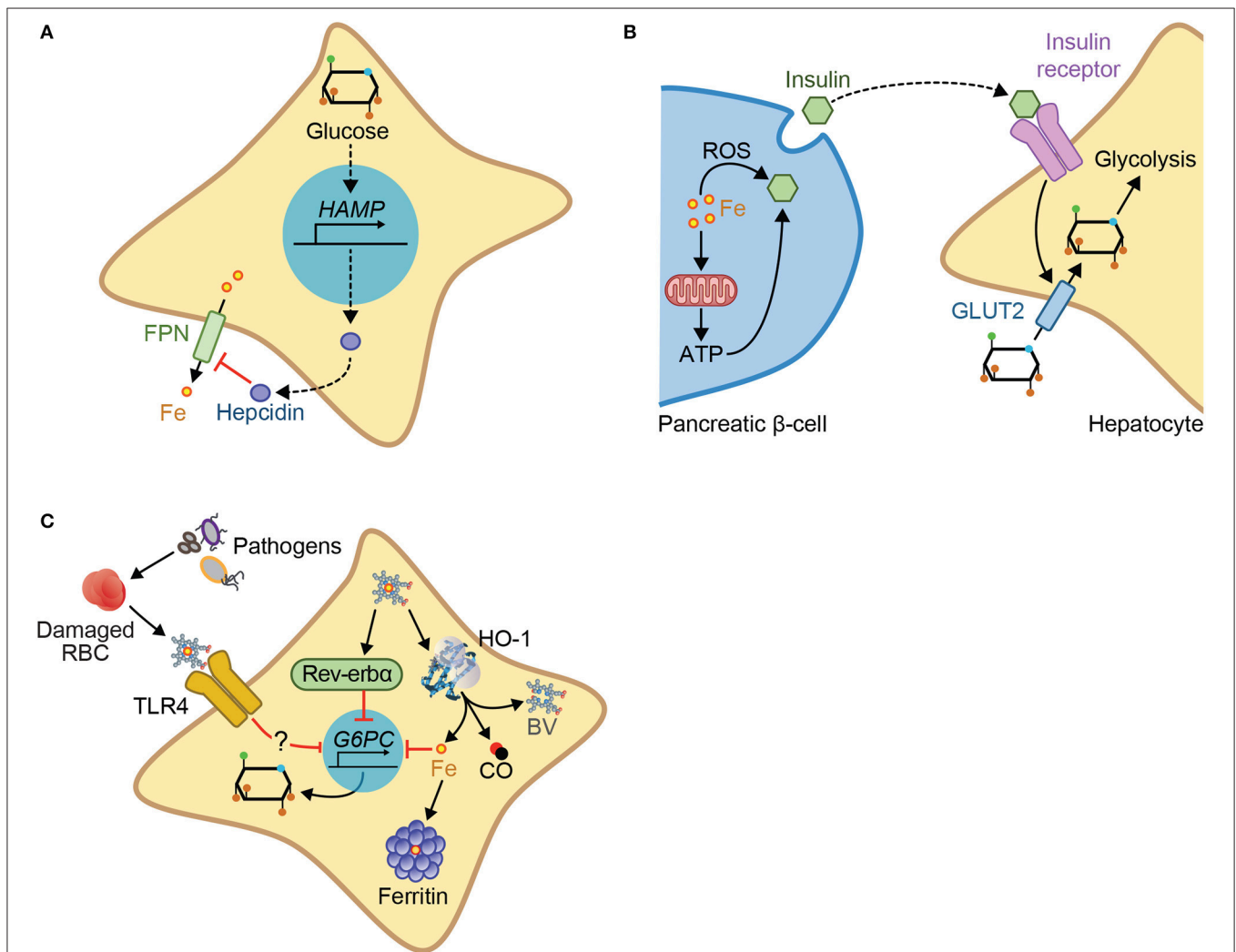
### Glucose Control of Innate and Adaptive Immune Function

Regulation of host glucose metabolism can impact on pathogens directly or indirectly, via modulation of immune-driven resistance mechanisms (84–86). Proliferation, differentiation, and effector function of immune cells is regulated by two major metabolic programs, namely, oxidative phosphorylation, and aerobic glycolysis (84–86). Signaling via PRR in macrophages or dendritic cells shifts metabolic flux from oxidative phosphorylation to aerobic glycolysis, a phenomenon known as the Warburg effect (87). Despite being less energetically effective, glycolysis generates pyruvate, nicotinamide adenine dinucleotide (NADH), and other metabolic intermediates used by major biosynthetic pathways (84, 86). This metabolic shift also promotes the pentose phosphate pathway, generating nicotinamide adenine dinucleotide phosphate (NADPH), a critical component of the NADPH oxidase (NOX) enzyme complexes, generating ROS involved in pathogen killing (84, 86, 88). In contrast to their microbicidal effector functions, other macrophage effector functions promoting tissue healing and regeneration rely primarily on oxidative phosphorylation (86, 88).

A marked increase in aerobic glycolysis is also a hallmark of T cell activation, together with a more modest induction of oxidative phosphorylation (86, 89), presumably accommodating the reduction in oxygen availability that arises during infections (85, 90). This metabolic reprogramming is orchestrated by a complex mechanism involving the store-operated  $\text{Ca}^{2+}$  entry

(SOCE), a key regulator of cellular calcium signaling (91), the hypoxia-inducible factor 1 $\alpha$  (HIF1 $\alpha$ ), a transcriptional master regulator of hypoxia, as well as the mammalian target of rapamycin complex 1 (mTORC1), a master regulator of cell growth (84, 86, 92). Of note, mTORC1 controls the expression of glycolytic genes in innate and adaptive immune cells via a mechanism involving HIF1 $\alpha$  (93–95). The relative impact of these metabolic pathways on the outcome of infections can be illustrated in the context of *M. tuberculosis* infection, where myeloid HIF1 $\alpha$  plays a critical role to induce the Warburg effect (96), supporting resistance to *M. tuberculosis* (97). Similarly, mice lacking HIF1 $\alpha$  in the myeloid compartment also fail to shift to aerobic glycolysis, succumbing to bacterial sepsis (98).

In contrast to effector T cells, memory T cells rely on oxidative phosphorylation to produce energy, using fatty acids to produce acetyl coenzyme A (acetyl-CoA) and fuel the Krebs cycle, via a mechanism known as fatty acid oxidation (FAO) (84–86). Moreover, recent work has shown that FAO in memory T cells, can occur not only via carnitine palmitoyltransferase IA (CPT IA)-dependent, but also independent mechanisms (99), suggesting that memory T cells are able to use a wide range of fatty acids in order to obtain energy. The switch between aerobic glycolysis and oxidative phosphorylation relies on a mechanism involving the transcription repressor Bcl-6 (100), which downregulates glycolytic genes and promotes the T and B cell differentiation toward the memory compartment (101–103).



**FIGURE 4 |** Mechanisms of iron-glucose metabolism cross-talk. Iron and glucose can cross-talk via different mechanisms: **(A)** Glucose increases expression of hepcidin, inhibiting cellular iron export via ferroportin. **(B)** Iron acts via the production of ROS or via mitochondrial respiration and subsequent ATP production, to promote insulin exocytosis by the pancreatic  $\beta$ -cells. Insulin binding to the insulin receptor in target cells, e.g., hepatocytes, promotes cellular glucose import via the glucose transporter 2 (GLUT2), and glycolysis. **(C)** In the context of infection, glucose metabolism can be regulated by heme via a pathway that involves TLR4, but which has not yet been fully described. Heme interaction with the nuclear receptor Rev-erba, downregulates the transcription of gluconeogenic genes including *G6PC*, the enzyme catalyzing the last step of gluconeogenesis. *G6PC* is also downregulated by iron produced via heme catabolism by HO-1, an inhibitory effect countered by ferritin.

Presumably, the combined effect of reduced glycemia and Bcl-6 expression are likely to promote effector to memory T cell transition in response to infection. Whether glucose availability impacts on immune-driven resistance mechanisms remains, to the best of our knowledge, to be determined.

## CROSS-TALK BETWEEN IRON AND GLUCOSE METABOLISM IN RESPONSE TO INFECTION

A functional interplay between iron and glucose metabolism has been established primarily in the context of metabolic diseases, such as porphyria (104, 105) or diabetes (106–108). For example, hepatic glucose production induces hepcidin expression (109, 110) (Figure 4A) and inhibits cellular iron export by ferroportin, leading to cellular iron overload and hypoferrremia (110). Conversely, cellular iron overload regulates insulin production in pancreatic  $\beta$ -cells (106, 111) and is thought to contribute critically to impair glucose metabolism in diabetic patients (112, 113) (Figure 4B). This interplay is probably operational in other pathologic conditions such as atherosclerosis (107) or  $\beta$ -thalassemia major (114).

More recently a crosstalk between iron and glucose metabolism has also been established in the context of infections (14, 115, 116). Namely, iron intake from diet leads to decreased pathogen virulence, without interfering with pathogen burden, favoring asymptomatic infection with the enteric pathogen *C. rodentium* (116). This occurs through a mechanism via which iron intake promotes insulin resistance, reducing glucose uptake by the intestine, and thus promoting glucose availability in the gut, leading to the suppression of virulence factors (116). Deregulation of host iron metabolism in response to polymicrobial infection compromises the establishment of disease tolerance to sepsis, via a mechanism that deregulates glucose metabolism (14, 117), thus also illustrating the crosstalk between iron and glucose. This pathologic mechanism is driven by labile heme, which plays a central role in the pathogenesis of sepsis (29). Namely, labile heme inhibits hepatic G6pase and consequently glucose production leading to hypoglycemia (14) (Figure 4C). This pathogenic effect has been linked functionally to a transcriptional repression of *g6pc1* gene (14). In support of this notion, mice lacking hepatic *g6pc1* develop lethal hypoglycemia in response to polymicrobial sepsis or heme administration (14). This suggests that hepatic glucose production is required to counter the hypoglycemia induced by labile heme (14). This is also consistent with the notion that deregulation of glucose metabolism plays a central role in pathogenesis of infectious diseases, including sepsis (10, 14, 80, 81, 118). This occurs via a mechanism that is not associated with modulation of host pathogen load (10, 14, 117), demonstrating that regulation of glucose metabolism controls the establishment of disease tolerance to infection (10, 14, 117).

The molecular mechanism via which labile heme induces hypoglycemia is not entirely clear but has been linked to signaling via Toll-like receptor 4 (TLR4) (14) (Figure 4C), a PRR that senses labile heme (119). This is consistent with the induction of hypoglycemia by TLR4 ligands, such as LPS (120).

Whether heme sensing by TLR4 mediates the development of hypoglycemia during polymicrobial sepsis was not established. The pathway through which heme represses *g6pc1* transcription (14, 121) is likely to involve the heme sensor and transcriptional repressor Rev-erba (121) (Figure 4C). Whether this mechanism is operational *in vivo* to repress hepatic glucose production and elicit hypoglycemia in response to infection remains to be established. It is possible as well that TLR4 and Rev-erba synergize to repress *g6pc1* transcription in hepatocytes.

Iron sequestration by ferritin counters heme-driven repression of *g6pc1* transcription, suggesting that heme represses *g6pc1* transcription via a mechanism involving iron (14). In keeping with this notion, polymicrobial infections in mice are associated with the induction of ferritin in the liver, which is essential to sustain hepatic glucose-6-phosphatase (G6Pase) expression and counter the development of lethal hypoglycemia (14, 122) (Figure 4C). Whether iron accumulation in hepatocytes synergizes with TLR4 and Rev-erba to repress *g6pc1* transcription remains to be established.

Regulation of hepatic glucose production by ferritin may be part of an adaptive response promoting the development of insulin resistance, presumably countering unfettered cellular glucose utilization in host tissues and allowing to restore normal blood glucose levels (123). This effect of ferritin should also contribute to prevent the development of hypoglycemia in response to infections.

## CONCLUSIONS AND FUTURE PERSPECTIVES

Resistance to infection is generally perceived as the predominant host defense strategy against infection. This dogma has been challenged by the recurrent observation that the severity of infectious diseases can at times be dissociated from host pathogen burden. In the last few years these observations have been interpreted as revealing disease tolerance as a critical host defense strategy against infection. This defense strategy relies on tissue damage control mechanisms controlling the metabolic output of host tissue and maintaining vital homeostatic parameters within a range compatible with host survival. This is illustrated for mechanisms regulating iron and glucose metabolism, which cross-talk to establish disease tolerance to infection. To what extent these tissue damage control mechanisms may be targeted therapeutically remains to be established.

## AUTHOR CONTRIBUTIONS

ARC wrote the manuscript with SW and MPS. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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