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Metabolic adaptations to infections at the organismal level

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Abstract

Metabolic processes occurring during host-microbiota-pathogen interactions can favorably or negatively influence host survival during infection. Defining the metabolic needs of the three players, the mechanisms through which they acquire nutrients, and whether each participant cooperates or competes with each other to meet their own metabolic demands during infection has the potential to reveal new approaches to treat disease. Here, we review topical findings in organismal metabolism and infection and highlight four emerging lines of investigation: how host-microbiota metabolic partnerships protect against infection, the competition for glucose between host and pathogen, the significance of infection-induced anorexia, and a redefinition of the role of iron during infection. We also discuss how these discoveries shape our understanding of infection biology and their likely therapeutic value.

The Hunger Games of Infection

Fulfilling energetic demands drives all biological functions. During infection, a host, its microbiota, and the infecting pathogen all have metabolic demands that must be met in order to guarantee their own survival; however, their ability to satisfy these demands is constrained by the energy intake of the host, which may be altered by the infection itself (1–4). Whether host, microbiota, and pathogen choose to compete or cooperate with each other to fulfill their energetic requirements shapes the outcome of infection (5–8). Over the last decade, there has been a reawakening of the intimate link between the immune system and metabolism that has spawned the field of **immunometabolism** (9). Most of the field has focused on the study of cellular immunometabolism, which investigates how metabolic changes at the cellular level lead immune cells to different fates (such as activation, proliferation, etc.) and regulate inflammation (10) (for extensive reviews on this subject, see [11, 12]). Although cellular immunometabolism is key to our understanding of inflammation, it does not encompass all the physiologies our metabolic system interacts with and that contribute to the outcome of infection. Here, we review recent discoveries in metabolic adaptations at the level of the whole organism and between all organisms involved: host, microbiota, and pathogen. We underscore four trending lines of investigation in the field and consider how their findings contribute to the ways in which we think about infection and the role of metabolism in disease development and therapy.

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Host-Microbiota Metabolic Partnerships Protect Against Infection

Microbiota-derived metabolites protect the host against infections

Through a long history of co-evolution, animals have developed a mutualistic (11) relationship with millions of gut microbes—the microbiota, which has allowed (33) both host and microbiota to thrive under different conditions, including the threat of pathogenic infection (13). One of the best characterized ways the microbiota (39) can promote protection against pathogenic infections is by mediating antagonistic defenses that prevent pathogen colonization or support pathogen killing (Figure 1). Microbiota can boost antagonistic defenses to harmful microbes via the production of metabolites, such as **short-chain fatty acids** (SCFAs) (7, 14–20). For example, in mice, the SCFA propionate promotes colonization resistance against *Salmonella* Typhimurium by disrupting bacterial pH homeostasis (21). Butyrate, another SCFA, directs colonocytes to consume O₂ through the **β-oxidation metabolic pathway**. By maintaining an anaerobic environment in the murine colon, butyrate favors the growth of beneficial Clostridia, obligate anaerobes which include butyrate producers, and limits the growth of pathogenic Enterobacteriaceae, facultative anaerobes that prosper in more aerobic environments (20). Additionally, by lowering O₂ concentration, butyrate promotes the stabilization of the hypoxia-inducible factor (HIF), a transcription factor that coordinates the expression of several components of the gut mucus layer—a key barrier to infection (19). Furthermore, butyrate can support pathogen killing by imprinting a non-inflammatory antimicrobial program in gut macrophages during their differentiation (via inhibition of histone deacetylase 3 [HDAC3]). Indeed, oral administration of butyrate in mice induced antimicrobial activity in intestinal macrophages and increased resistance to various enteropathogens. This suggests that butyrate supplementation may represent a strategy to boost host defenses without the damaging effects of inflammation, although this remains to be further tested (22).

Host-microbiota co-evolution has shaped the ecology of the mammalian intestinal microbiota. Changes in the composition of the microbiota, a condition called **dysbiosis**, are associated with various disease states, such as inflammatory bowel disease, allergic disorders, obesity, Type 1 diabetes mellitus, autism, and colorectal cancer. Beyond pathogenic infection, beneficial metabolites guard the host from drifting toward a dysbiotic microbiota. For instance, in mice, the microbiota-associated metabolite taurine, a bile acid conjugate, activates the NLRP6 **inflammasome**, leading to the production of antimicrobial peptides (AMPs) in the colonic mucosa via the NLRP6-IL-18-AMP axis. Administration of taurine to wildtype mice induced compositional changes in the intestinal microbiota that did not occur upon taurine administration to *Nlrp6*^{-/-} mice. By producing taurine, wildtype microbiota turn on an immune program that regulates intestinal microbial composition, suppressing the development of dysbiotic microbiota and maintaining the homeostatic microbiota ecology (15).

In addition to antagonism, a host relies on cooperative defenses that work to promote host health (23). Cooperative defense approaches include **disease tolerance**, which induces tissue-protective programs, and **anti-virulence mechanisms**, which promote pathogen fitness within the host by dampening its virulent behavior (23–25). Both disease tolerance

and anti-virulence tactics promote host health without affecting the ability of a microbe to occupy the host niche or replicate within it (5, 23, 25, 26). Recently, microbiota-derived metabolites have been shown to support disease tolerance mechanisms (in addition to antagonistic defenses) (Figure 1). For example, experimental work has shown that oral administration of the metabolite desaminotyrosine (DAT) protects mice from influenza virus infection by lessening lung immunopathology in addition to increasing type I interferon expression, which enhances immunity to influenza (16). A parallel study also established that SCFAs boosted survival of influenza-infected mice. In this model, SCFAs were shown to simultaneously damp airway immunopathology via restriction of excessive neutrophil influx—which can lead to tissue damage—and augment CD8⁺ T cell effector function by enhancing cellular metabolism (7). In future work, it will be important to determine how microbiota-derived metabolites can promote anti-virulence defenses against members of the microbiota or invading pathogens.

Recently, it has become evident that metabolite-conferred protection can sometimes be attributed to the presence of a single bacterial species with rare biosynthetic capacity within the host (16, 17). It is well established that the widespread overuse of antibiotics decimates intestinal microbial communities, and this has been associated with increased susceptibility to diverse pathogens (27). *Clostridium difficile* is a leading cause of nosocomial infectious diarrhea, increasing morbidity and mortality in hospitalized patients. The principal risk factor for *C. difficile* infection is prior antibiotic use (28). Using an elegant approach that combined mouse models, clinical studies, metagenomic analyses, and mathematical modeling, a recent study demonstrated that the bacterium *Clostridium scindens*, a resident of both the human and murine gut, converted primary bile acids into secondary bile acids, which in turn inhibited the growth of *C. difficile* (17). Antibiotic-induced loss of *C. scindens* strongly correlated with increased susceptibility to *C. difficile*, and reintroduction of *C. scindens* alone into *C. difficile*-infected mice improved *C. difficile* infection outcome, ameliorating weight loss and mortality, thus fulfilling **Koch's postulates** in reverse—for a microbe with a positive health effect. These findings highlight an often overlooked issue in the discussion about the overuse of antibiotics: antibiotic misuse not only pushes the rise of antibiotic resistance in pathogens, but it also leads to the elimination of clinically relevant, beneficial microbes, placing already sick patients at greater risk of acquiring an infection. Future work is required to identify other bacterial species with uniquely protective biosynthetic functions. Characterizing these beneficial microbes may help ensure that we can avoid eliminating them during treatment. Alternatively, in cases where treatment does eradicate these populations, it may be possible to take measures to resupply patients with uniquely beneficial microbes post-treatment.

Protection by microbiota is highly dependent on host diet

An emerging trend in the field is that microbiota-conferred protection is often conditional on host diet. Beneficial microbiota-derived metabolites are generated only after consumption of specific nutrients. For example, beneficial SCFAs, such as butyrate and propionate, originate from the fermentation of fiber in the colon (29). Similarly, human microbiota produce DAT during flavonoid metabolism (30). This finding raises some issues. First, it is possible that studies looking at the effects of specific gut microbes may have missed the potential benefits

of these microbes in the absence of the right diet. Another point of concern relates to the effect of Western diet on the ability of the microbiota to protect the host from harmful microbes. Not only are Western diets typically low on fruits and vegetables (sources of fiber and flavonoids), but they are also correlated with a substantial decrease in gut microbial diversity, which could plausibly eliminate health-promoting bacteria from the gut (Figure 1) (31, 32). Furthermore, it is becoming increasingly clear that the virulence of a microbe can be largely dependent on substrate availability for metabolism (8, 24, 33, discussed later in the text). If protection is diet-dependent, and the appropriate diet is missing, how can we still receive the benefits from the microbiome? Deciphering the “metabolite code” that microbiota use to protect the host from infection may one day help us to partially bypass the requirement for particular microbiota and diet. For example, it is reasonable to speculate that the flu vaccine might one day be coupled with direct supplementation of specific metabolites, such as DAT, in order to immunize at-risk patients but also prime their immune systems and reduce immunopathology should the vaccine not be a good match for that year’s circulating viral strain. Another pressing reason to understand the microbiota’s metabolite code comes from the discovery that dysbiotic microbiota use metabolites to hijack the host and foster their own growth. For instance, in mice, the dysbiotic microbiota-associated metabolites spermine and histamine have been shown to suppress the NLRP6 inflammasome in intestinal epithelial cells, lowering the production of AMPs in the colon. By producing these metabolites, dysbiotic microbiota inhibited the antimicrobial program that constrains them and promoted their own growth in the host (15). Understanding how dysbiotic microbiota use metabolites to take over the host may lead to novel therapies that directly target the production of these metabolites to treat or prevent dysbiosis-driven diseases.

Beneficial microbes go out of their way to protect the host

In invertebrates, microbial symbionts that inhabit parts of the body beyond body surface barriers and that can reside in intracellular niches are well appreciated (34). By contrast, resident microbes of the vertebrate host are traditionally believed to be extracellular and only inhabit barrier surfaces. Penetration of these barriers by the microbiota has been assumed to always result in disease; however, this view has been challenged by recent studies. Members of the *Alcaligenes* spp. can colonize gut associated lymphoid tissues (GALT) of healthy mammals, including the Peyer’s Patches and mesenteric lymph nodes (35, 36). Whether colonization of GALT by *Alcaligenes* spp. provides benefits to the host remains to be determined.

Recently, Schieber et al. showed that a particular gut microbiota-resident *E. coli* strain protected mice from infection-induced wasting (37). Mice carrying *E. coli* O21:H+ did not show weight loss, adipose tissue, or skeletal muscle wasting when infected orally with *S. Typhimurium* compared to infected mice that did not carry this particular *E. coli* strain in their microbiome. Protection from infection-induced wasting was associated with challenge-induced translocation of *E. coli* O21:H+ from the gut to the **white adipose tissue (WAT)** and the activation of the NLRC4 inflammasome, which correlates with increased production of IGF-1 by the WAT. The mechanism through which this *E. coli*’s host-protective behavior is triggered remains to be elucidated. New findings from other studies suggest that the host

may indirectly relay cues that it has become infected to its microbiota (5, 38, 39, discussed later in the text), perhaps providing a clue as to how the protective behavior of *E. coli* O21:H+ is induced. A trend that is emerging from recent host-microbe studies is that the adipose tissue is a common site for bacterial, viral, and parasite colonization (40–42). While the purpose for these microbes to colonize this tissue remains to be elucidated, the work by Schieber et al. suggests that the fat may serve as a hub for microbes to orchestrate healthy physiological interactions in the host. Thus, identifying additional microbes that translocate beyond host barriers to induce beneficial responses at distal sites will be important for future studies in the host-microbe field.

Hosts must feed beneficial microbes or else...

Microbiota can provide a wide variety of benefits and protection from infection, but the host must return the favor by supplying the microbes with the right nutrients. Failure to do so can have negative consequences for the host (Figure 1). For example, in response to dietary fiber deficiency, human gut microbiota have been shown to degrade the colonic mucus barrier, thereby increasing pathogen susceptibility (43). Host anorexia is a common feature of infections (1–4). While it can provide an advantage to the host during some infections, anorexia imposes a stress on intestinal microbes, as they also experience nutrient deprivation (44). Recently, a noteworthy study elucidated a mechanism by which the host can sustain its microbiota during the anorexic period of infection (38). The authors showed that systemic exposure to Toll-like receptor (TLR) ligands resulted in rapid fucosylation of small intestine epithelial cells (IECs) in mice. This process required sensing of TLR ligands, production of interleukin (IL)-23 by dendritic cells, activation of innate lymphoid cells, and expression of fucosyltransferase 2 (Fut2) by IL-22-stimulated IECs. Following the shedding of fucosylated proteins into the gut lumen, fucose was metabolized by the microbiota. In the absence of fucosylation, microbiota increased their virulence. In contrast, microbiota that were provided nutrients through fucosylation helped their hosts regain weight faster following immune stimulation. This demonstrates that this fucosylation mechanism serves as an anti-virulence defense strategy (23–24). Of note, dysbiotic microbiota are known to lower IL-22 production in mice (18). Given that IL-22 is required for fucosylation, this raises the possibility that only wildtype microbiota promote their upkeep during infection-induced anorexia—although this remains to be tested. Finally, it has been demonstrated that consumption of dietary fiber following influenza infection can improve survival in mice. The SCFA butyrate was found to be the source of this effect. (7). Recent work has highlighted the benefit of feeding the host during influenza infection, as it too can promote host survival (45, discussed later in the text). It may be that feeding the microbiota as well as the host might further improve the outcome of some infections.

The Glucose Wars

Glycolysis potentiates immune function

Upon infection, many types of immune cells shift from oxidative phosphorylation to aerobic glycolysis, a shift known as the **Warburg effect** (46–51). Although glycolytic metabolism is a comparatively inefficient pathway for the generation of cellular ATP (only two molecules of ATP per unit of glucose), it offers a key benefit in that it provides biosynthetic

intermediates for the synthesis of nucleotides, amino acids, and fatty acids. This is presumably the reason why a majority of immune cells, which must quickly replicate and synthesize large numbers of effector molecules, enter glycolysis following some infections (12). This switch to glycolysis is critical for a successful host response to infection and has been documented in both animal models and clinical settings (Figure 2) (48, 49, 52, 53).

While glycolysis is an important metabolic driver of immune function, excessive immune activation stemming from enhanced glycolytic activity can lead to organ damage and increased mortality. For example, in mice, polymicrobial sepsis has been shown to promote glycolytic metabolism, which plays a role in sepsis-induced cardiomyopathy and mortality (54). In this model, modulation of glycolytic metabolism by administration of 2-Deoxy-D-glucose (2-DG), which inhibits glycolysis, was found to markedly decrease proinflammatory cytokine production and myocardial cell apoptosis while improving cardiac function and survival. Regulating excessive immune activation via metabolic reprogramming is seen as a promising approach to treating a variety of immune-related pathologies; indeed, there are already a number of studies showing the viability of metabolic inhibitors as therapeutic tools (55, 56).

Glycolysis promotes pathogen virulence

Pathogens also regulate their metabolism during the course of infection. Specifically, a variety of microbes enter glycolysis, which has been shown to be required for bacterial and fungal virulence (Figure 2) (6, 57–60). Metabolic adaptations in pathogens that are necessary to enter virulence programs may offer a prime target for the generation of new antimicrobials, as pathogens that are not able to alter their own metabolism are typically rendered avirulent.

Host and pathogen battle for glucose during infection

As both immune cells and pathogen enter glycolysis early during the course of diverse infections, an immediate war for glucose erupts between host and pathogen (Figure 2) (6, 60). Although it is possible that pathogens upregulate glycolytic genes to facilitate the biosynthesis of molecules required for invasion and growth, it is also conceivable that they do so to set a trap for the host. Upon infection with *Candida albicans*, upregulation of glycolysis in both host macrophages and pathogen sets up a competition for glucose between the two. Because *C. albicans* outcompetes host macrophages for glucose—despite remaining metabolically plastic during infection—the Warburg effect becomes a liability for macrophages during microbial challenge, and starved macrophages die (6). Of note, glucose supplementation slows disease progression in this mouse *C. albicans* infection model, pointing to a new potential avenue of treatment for systemic candidemia.

To eat, or not to eat, that is the question

Anorexia is a host sickness behavior

Acute infections are associated with a set of stereotypic behavioral responses, such as anorexia, lethargy, somnolence, fever, and social withdrawal, among others. Collectively

termed **sickness behaviors**, these behaviors are highly conserved across species. Emerging evidence suggests that sickness behaviors are, in fact, evolved strategies to favor host survival during infection (61–63). Today's standard biomedical practices interfere with many sickness-induced behaviors, including anorexia (64). Because of this, it is essential that we understand the mechanisms that lead to the induction of anorexia, as well as the context in which anorexia proves beneficial or harmful to the host during infection.

No two infections are the same

Recently, studies have tackled the question of whether anorexia is beneficial or detrimental to the outcome of infection, arriving at different conclusions depending on the infection studied (Figure 3) (1, 45, 65–67). For instance, one study showed that anorexia was protective while feeding was detrimental in a *Listeria monocytogenes* murine infection model (68). In follow up work, Wang et al. showed that glucose supplementation alone was sufficient to mediate lethality in this model, and that dosing with 2-DG, an inhibitor of glycolysis, promoted survival of the mice (45). The authors found that glucose promoted neuronal reactive oxygen species (ROS) and seizure-induced death during LPS-induced inflammation. However, when comparing this bacterial LPS model to a model of systemic viral infection, the authors observed opposite results. During influenza infection, glucose supplementation protected against mortality, while blocking glucose utilization via 2-DG proved lethal. Generalizing their findings via the use of the Poly(I:C) model of viral inflammation, the authors subsequently demonstrated that glucose utilization prevents unfolded protein response (UPR)-mediated neuronal damage during viral inflammation. Of note, in both the viral and bacterial models, the effect of glucose was independent of the magnitude of the inflammatory response and pathogen load. Instead, the authors identified contrasting metabolic requirements tied to cellular stress adaptations in the brain as essential for tolerance to different inflammatory states (45). Their results demonstrate that metabolic adaptations during infection serve not only to potentiate immune function (as discussed in the previous section), but also to promote disease tolerance by supporting infection-induced cellular stress adaptations in organs such as the brain, which are critical to survive infection (Figure 3).

A particularly noteworthy aspect of the work by Wang et al. (45) is that it sheds light on the very fine balance that the host must strike in tuning metabolic adaptations to deal with infection. On the one hand, numerous studies have indicated that the host must upregulate a glycolytic program to potentiate immune function and promote antagonistic defenses during infection (46–51). On the other hand, the host must ensure that this pro-glycolytic drive does not completely hinder its ability to promote disease tolerance during infection, which appears incompatible, in some cases, with this pro-glycolysis push, as evidenced by the survival-promoting effect of 2-DG during the course of *L. monocytogenes* infection (45). However, partially blocking glycolysis during infection, as previously proposed by others, is not a one-way-fits-all approach to lessening immunopathology (54). Based on the findings from the viral infection and Poly(I:C) model discussed above, blocking glycolysis can prove to be gravely detrimental in the case of some infections, as it may block the ability of the host to prevent UPR-mediated neuronal damage (45). It is becoming increasingly evident that differential immune responses must be paired with specific metabolic programs to

support the energetic demands of these inflammatory reactions as well as the adaptations to particular forms of cellular stress induced by them (Figure 3). While it may be possible to treat immunopathology via metabolic manipulation, it is important to remember that the same strategy will not necessarily work for all infections—a likely consequence of the fact that distinct pathogens elicit vastly different physiological responses in the host as they affect the host in unique ways (69–71).

Finally, it is essential to highlight that the role of anorexia during infection is not a simple dichotomy between ‘feeding’ a viral infection and ‘starving’ a bacterial infection. Indeed, the effects of anorexia have been demonstrated to be pathogen-specific. For example, in the case of *Salmonella*, another bacterial infection, nutritional supplementation has been shown to promote host survival (67). As more studies on infection-induced anorexia reveal which infections benefit from nutritional supplementation and which do not, it will be interesting to determine what factors, if any, are common to infections that benefit from anorexia and how this group is different from infections where anorexia is detrimental.

Pathogen-mediated appetite control

During infection, pathogens become reliant on the energy intake of their hosts. Because of this, the effect of a fasting metabolism on microbial virulence may also dictate whether anorexia confers any benefit to the host following infection. It has been proposed that anorexia has a negative effect on pathogens, promoting a metabolic environment that deprives them from essential nutrients to the benefit of the host (62). However, it is also plausible that the fasted state may trigger increased pathogen virulence, as it is known that microbes alter their metabolic capacity and foraging strategies in order to adjust to nutrient scarcity (72, 73). A study recently described an example of the latter scenario. Rao et al. assessed how infection-induced anorexia affected host mortality in a *Salmonella* Typhimurium transmissible model of infection (67). The authors showed that the *S. Typhimurium* effector SlrP inhibited the infection-induced anorexic response, thus lowering bacterial virulence and promoting survival of the host. Mice infected with the *S. Typhimurium* *slrP* strain consumed significantly less food and displayed increased mortality compared to mice infected with the wildtype strain of *S. Typhimurium*. This effect was independent of pathogen burden. Instead, the authors demonstrated that SlrP inhibited inflammasome activation and IL-1 maturation, which can induce anorexia, in myeloid cells of the small intestine, preventing the induction of the anorexic program in the hypothalamus that is dependent on the vagus nerve. Failure to inhibit IL-1 β and the anorexic response resulted in increased anorexia, extra-intestinal *S. Typhimurium* dissemination, and increased virulence of the pathogen—at the expense of pathogen transmission to new hosts (67). This study demonstrates that microbes, including pathogens, have evolved mechanisms that modulate host behavior to promote both health in their hosts and their own transmission (Figure 3).

While the selection for sickness-induced behaviors likely occurs at the individual host level—driven by the benefits they confer to the individual host, the work of Rao et al. suggests that the evolution of anorexia as a sickness behavior may also serve to provide protection at the population level from certain types of infection (67). In the case of *S. Typhimurium*

infection in mice, anorexia is maladaptive for the individual host. However, when anorexia is developed by an individual mouse, protection is extended to other mice, as the anorexic mouse is less likely to transmit the pathogen. Therefore, similar to social withdrawal, infection-induced anorexia can serve to confine the spread of a pathogen (74). Moreover, this study highlights the elegant approach of using transmissible models of infection to identify novel strategies that promote individual host survival (67). If a host physiological response, such as anorexia, creates trade-offs between pathogen virulence and transmission, then it is likely that pathogens, which have co-evolved with animals to favor their own transmission, may have figured out different strategies, such as inhibition of anorexia, to overcome these constraints. Thus, it is plausible that various microbes possess mechanisms and or effectors (similar to *Salmonella* Slrp) that simultaneously promote individual host health and their own transmission. By studying how microbes promote host health to promote their own transmission, we might learn how to bypass these evolutionary constraints to promote individual host survival. Remarkably, this knowledge may be exploited to our benefit beyond its original scope. For example, it may be possible to engineer microbes to stimulate host appetite in an effort to treat conditions such as anorexia nervosa or induce anorexia to counteract an overactive appetite (67).

Cross-talk between iron and glucose metabolism

Expanding the role of iron during infection

Iron is an essential nutrient. The requirement for iron is based on its role in a myriad of metabolic processes, including electron transport, DNA synthesis, and protection from oxidative stress. Because bacteria require iron in order to replicate, the historical view of iron in the field has been that iron is something to be fought over between host and pathogen—an eternal race between a host trying to hide its iron and a pathogen that is determined to steal it in order to grow (Figure 4) (75). Recent work is changing this exclusive view. For example, regulation of host iron metabolism was found to be crucial to confer disease tolerance in murine models of malaria and polymicrobial sepsis (76, 77). Moreover, iron supplementation is known to confer protection and even a survival advantage in some infections (5, 78). Furthermore, it was recently shown that elevated heme concentrations compromise antagonistic defenses to infection—independently of heme-iron acquisition by pathogens—by strongly inhibiting macrophage phagocytosis, and that heme alone can also induce programmed necrosis in macrophages (79, 80). Altogether, these findings suggest that the role of iron during infection is far more complex than originally envisioned, a likely result of how different pathogens affect host physiologies in unique ways (Figure 4).

To survive, you must cooperate

When faced with a pathogenic infection, what allows some hosts to survive while others perish? In a recent study, Sanchez et al. proposed using of the concept of **lethal dose 50** (LD50) as a means to mechanistically answer this question. Using this approach, the authors identified a novel strategy by which some hosts create a metabolically favorable environment for the pathogen, thus enticing the microbe to forsake its virulence program (5). The authors challenged mice orally with an LD50 dose of *Citrobacter rodentium* and found that while 50% of mice died from this challenge, there was no difference in pathogen

load between the dying and surviving groups. After performing RNA-seq on the livers of infected animals, they determined that iron metabolism genes were upregulated in the livers of surviving hosts. Feeding iron-supplemented diets to infected mice conferred complete protection against the infection. The authors demonstrated that dietary iron induced **insulin resistance** (IR), increasing glucose concentrations in the intestine, which was necessary and sufficient to suppress pathogen virulence. Moreover, iron administration drove the selection of attenuated *C. rodentium* strains, revealing that cooperative metabolic strategies can drive pathogens toward commensalism (5). This study uncovered how hosts not only developed mechanisms to eliminate pathogens and tolerate the damage brought upon by infection, but they also evolved strategies that allow them to lower the virulence of a pathogen via metabolic cooperation. The idea of cooperative defenses represents a radical new approach to treating infectious diseases, with the potential to open new avenues of treatment in the clinic—especially in light of the growing spread of antibiotic resistant pathogens (5).

The work of Sanchez et al. elegantly demonstrated the value of using an LD50 approach to uncover novel mechanisms to survive infection (5). This strategy can be applied to other infectious and non-infectious disease models to understand variation in susceptibility to disease and identify new interventions to promote host survival. Finally, because acute IR is a common response to infection, the results of this study may suggest that one of the functions of acute IR is to increase the availability of glucose to the gut microbiota in order to prevent the upregulation of their virulence programs (as described in an earlier section) (38, 81).

The link between glucose and iron metabolism

While Sanchez et al. showed that tissue iron sequestration regulates blood glucose concentration by inducing IR during infection (5), a parallel study proposed that iron sequestration controls glycemia by inducing ferritin to maintain liver gluconeogenesis during sepsis (77). Nevertheless, the conclusions of Sanchez et al. are supported by a separate investigation that determined that heme-oxygenase-1 (*Hmox1*), a gene found to be upregulated in the surviving LD50 population as well as the iron-supplemented mice in the former study, induced IR during chronic metabolic inflammation in both mice and humans (82). Indeed, *Hmox1* has been reported to induce cooperative defenses in different infection models (83–85). In those studies, its survival-promoting effects were attributed to detoxification functions. However, the study by Sanchez et al. suggests that the means by which *Hmox1* promotes cooperative defenses is IR induction, which may act to increase the availability of glucose to non-insulin dependent organs (e.g., brain, etc.) as well as to sustain the normal microbiota during infection.

Concluding Remarks

Metabolic interactions during infection are a true *ménage à trois* (household of three) between host, microbiota, and pathogen. In this household, host-microbiota metabolic partnerships protect the host from the deleterious effects of infection. In parallel, a war for glucose erupts between host and pathogen, with the host seeking glucose to potentiate its immune response, while the pathogen requires it to activate its virulence program.

Complicating these interactions, infection-induced anorexia is making the household very hungry, and balancing the host's metabolic needs with those of the microbiota and pathogen—so as to lower their virulence—is a difficult task, albeit one that is key in order for the host to survive in this household. To date, the vast majority of studies examining metabolic adaptations during infection have focused on one or two members of this household, rarely looking at the interactions between all three. However, it is essential that we recognize that metabolic adaptations during infection have not evolved in isolation, and all three players need to be considered when thinking about the ways in which these interactions play out (see outstanding questions). Furthermore, while the field of immunometabolism has the potential to uncover many novel avenues to promote health and treat infections, the scope of future studies needs to be expanded to the whole organismal level to truly understand how metabolic responses during an infection shape host outcome.

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Figure 1: Host-microbiota metabolic partnerships protect the host against infections
 Wildtype microbiota produce an array of beneficial metabolites that protect the host from infection and dysbiotic microbiota. However, this benefit is highly dependent on the presence of the right diet, which serves to maintain an abundance of health-promoting microbes and provides the substrates needed for the generation of beneficial metabolites.

Figure 2: Host and pathogen duel for glucose during infection

Many types of immune cells switch to aerobic glycolysis upon infection, a necessary change to potentiate the immune response. In parallel, several pathogenic microbes also enter glycolysis following infection, and this change is largely required to induce their virulence programs. This sets up a competition for glucose between host and pathogen.

Figure 3: The effects of anorexia during infection are pathogen-specific

Anorexia, a host sickness behavior, can be beneficial or detrimental to the host depending on the infection, presumably as a result of how different infections affect host physiologies in unique ways.

Figure 4: New perspectives on the role of iron during infection

Recent studies suggest that the role of iron during infection is more complex and context-dependent than the originally envisioned, simple tug-of-war.