Targeting immunometabolism in host-directed therapies to fungal disease

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**List of abbreviations**

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<th>Abbreviation</th>
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<tbody>
<tr>
<td>2-DG</td>
<td>2-deoxy-D-glucose</td>
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<tr>
<td>AMP</td>
<td>Adenosine monophosphate</td>
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<tr>
<td>ATF3</td>
<td>Activating transcription factor 3</td>
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<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guérin</td>
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<td>COVID-19</td>
<td>Coronavirus disease 2019</td>
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<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>GSK3β</td>
<td>Glycogen synthase kinase 3β</td>
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<td>HIF-1α</td>
<td>Hypoxia-inducible factor-1α</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>IDO1</td>
<td>Indoleamine-2,3-dioxygenase 1</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<td>IRG1</td>
<td>Immune-responsive gene 1</td>
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<td>LAP</td>
<td>LC3-associated phagocytosis</td>
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<td>LPS</td>
<td>Lipopolysaccharide</td>
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<td>MPLA</td>
<td>Monophosphoryl lipid A</td>
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<tr>
<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
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<td>NO</td>
<td>Nitric oxide</td>
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<tr>
<td>NRF2</td>
<td>Nuclear factor erythroid 2–related factor 2</td>
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<tr>
<td>PFKFB3</td>
<td>6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3</td>
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<tr>
<td>PI3K</td>
<td>Phosphatidylinositol-4,5-bisphosphate 3-kinase</td>
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<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
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<tr>
<td>SDH</td>
<td>Succinate dehydrogenase</td>
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<tr>
<td>TCA</td>
<td>Tricarboxylic acid</td>
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<tr>
<td>TLR4</td>
<td>Toll-like receptor 4</td>
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Abstract

Fungal infections affect over a billion people and are responsible for more than 1.5 million deaths each year. Despite progress in diagnostic and therapeutic approaches, the management of severe fungal infections remains a challenge. Recently, the reprogramming of cellular metabolism has emerged as a central mechanism through which the effector functions of immune cells are supported to promote antifungal activity. An improved understanding of the immunometabolic signatures that orchestrate antifungal immunity, together with the dissection of the mechanisms that underlie heterogeneity in individual immune responses, may therefore unveil new targets amenable to adjunctive host-directed therapies. In this review, we highlight recent advances in the metabolic regulation of host-fungus interactions and antifungal immune responses, and outline targetable pathways and mechanisms with promising therapeutic potential.

Keywords
Immunometabolism, fungal disease, host-directed therapy, antifungal immunity, immunotherapy
Introduction

Fungal infections affect over a billion people and are responsible for more than 1.5 million deaths each year [1]. Recent advances in critical care medicine, including solid organ and stem-cell transplantation, chemotherapy, and broad-spectrum antibacterial or immunomodulatory therapy, are contributing to the increasing incidence of severe fungal infections. In developing countries, the immune dysfunction resulting from HIV infection is also associated with susceptibility to fungal disease, while endemic primary fungal pathogens can also cause disease in immunocompetent individuals. In addition, the frequency of life-threatening fungal infections that occur in the context of viral pneumonia, e.g., influenza or COVID-19, is also rapidly expanding [2, 3]. Licensed vaccines are still not available, and despite progress in diagnostic and therapeutic approaches, the management of severe fungal infections remains a challenge associated with high mortality rates [4] and healthcare costs [5]. These numbers emphasize the urgent need to further elucidate the pathogenetic mechanisms involved in susceptibility to infection and foster the development of more effective diagnostic and control measures for fungal infections.

In recent years, the identification of several factors and mechanisms related to the immune response has provided exciting developments to our understanding of the pathogenesis of fungal infections [6, 7]. The reprogramming of cellular metabolism has recently emerged as a central mechanism through which the effector functions of immune cells are supported during host antifungal defense [8]. An improved understanding of the immunometabolic signatures that orchestrate antifungal immunity may therefore reveal new targets amenable to adjunctive host-directed therapies, which are currently limited to cytokines, monoclonal antibodies, or cellular immunotherapy [9]. In this review, we discuss recent findings on the immunometabolic signatures activated in response to fungal infection and highlight targetable pathways and mechanisms that show promising potential as adjuncts for host-directed therapies.

Metabolic regulation of the host-fungus interaction

Metabolism is a determining factor of immune cell function [10]. Upon infection, immune cells sense molecular patterns from pathogens and remodel their metabolic outputs beyond their normal energy requirements (Figure 1). Different metabolites are used as signaling molecules, enzymatic
cofactors, and substrates that support the activation of immune effector functions, including phagocytosis, cytokine production, cell surface receptor expression, antigen presentation, and the control of long-term responses. In turn, pathogens can sense the metabolites produced by activated immune cells and reshape their ligand repertoire to hide from or subvert the immune response [11]. These observations highlight the profound impact of coordinated metabolic networks on the outcome of the host-pathogen interaction.

Glucose metabolism of immune cells is at the center of antifungal immune responses, potentiating the production of proinflammatory cytokines and other inflammatory mediators, and reactive oxygen species (ROS) [8]. In the context of fungal infections, this metabolic route in immune cells has been predominantly studied in response to *Candida albicans* [12-16] but has also recently been shown to occur during infection with *Aspergillus fumigatus* [17] and *Cryptococcus gattii* [18]. Although glycolysis is often induced in a context of reduced oxidative phosphorylation, leading to the so-called Warburg effect [16], human monocytes challenged with *C. albicans* are nonetheless endowed with functional oxidative phosphorylation [13]. This implies that immunometabolic signatures vary in intensity and nature according to the microbial insult or the receptor involved [19]. Likewise, the metabolic remodeling in response to infection with *C. albicans* also depends on the fungal morphotype [13]. While monocytes stimulated with the yeast form rely on glycolysis and glutaminolysis to mount cytokine responses, hyphal stimulation primarily drives the activation of glycolysis. These divergent profiles are likely due to the variable expression of the β-glucan polysaccharide in the yeast and hyphal cell wall. In this regard, β-glucan masking was shown to be induced by lactate-mediated signals that control the expression of cell wall-related genes [20]. Moreover, by taking advantage of its efficient metabolic fitness, *C. albicans* exploits the terminal commitment of macrophages to glycolysis by competing for and depleting available glucose, ultimately leading to rapid cell death [16]. These findings depict crucial virulence traits from fungi that, by exploiting or subverting host metabolism, contribute to evasion from the immune system (Figure 1).

In contrast to *C. albicans*, the expression of β-glucan in the cell wall of *A. fumigatus* appears instead to be largely dispensable to the activation of glycolysis in macrophages [17]. Instead, the phagosomal release of melanin from the surface of conidia was shown to regulate calcium-dependent signals leading to enhanced glycolysis through the activation of mammalian target of rapamycin
(mTOR) and hypoxia-inducible factor-1α (HIF-1α) (Figure 1). These findings are in line with the requirement for HIF-1α to the modulation of cytokine release by human dendritic cells upon infection with *A. fumigatus* [21] and the non-redundant role of HIF-1α in mouse models of aspergillosis [22]. Of note, the metabolic reprogramming induced by fungal melanin appears to occur regardless of its recently identified receptor MelLec [23]. Instead, the germination process associated with the active removal of melanin within the phagosome is required for host cells to rewire their metabolism. In support of this, germination has been shown to promote fungal clearance, as faster-growing CEA10-derived strains are cleared more efficiently *in vivo* than slower-growing Af293-derived strains [24]. This enhanced fungal elimination could thus be explained by cell wall rearrangements culminating with melanin release during germination and the activation of host glycolysis. Whatever the mechanism(s), the efficient regulation of glycolysis is required for resistance to aspergillosis in humans. This is illustrated by the recent finding that genetic variation in 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), a critical regulator of glucose metabolism, was found to impair antifungal effector functions of macrophages and predispose recipients of allogeneic hematopoietic stem-cell transplantation to the development of invasive pulmonary aspergillosis [25]. PFKFB3 is upregulated in bacterial infections and PFKFB3-driven glycolysis in macrophages is critical for antiviral defense [26], pinpointing this gene as a possible therapeutic target across infectious diseases. Moreover, the similar regulation of glycolysis in immune cells in response to different infectious agents [27] highlights the attractive possibility of exploiting genetic variants in metabolic genes and their effects on immunometabolic signatures as a tool to identify and stratify the patients most at risk of infectious diseases.

**Immunoregulatory functions of host metabolites in fungal infection**

The metabolic switch to glycolysis results in the accumulation of several intermediates of the tricarboxylic acid (TCA) cycle that act as signals to link metabolism and immunity. In recent years, the metabolite itaconate has been explored for its broad immunomodulatory properties. Activated myeloid cells display enhanced expression of the immune-responsive gene 1 (IRG1) mitochondrial enzyme, which catalyzes the decarboxylation of the TCA cycle intermediate cis-aconitate to itaconate [28]. The molecular mechanisms under control by itaconate vary, but the net function is thought to be anti-
inflammatory. Itaconate inhibits the succinate dehydrogenase (SDH), which is both an enzyme of the TCA cycle and the complex II of the electron transport chain, leading to succinate accumulation and impaired mitochondrial respiration, and suppressing the production of inflammatory cytokines [29]. Moreover, itaconate enables the activation of the transcription factors NRF2 and ATF3, and the increased expression of downstream genes with antioxidant and anti-inflammatory properties, and the modulation of type I interferon responses [30].

Itaconate plays an important role across several infections, decreasing tissue injury in a mouse model of tuberculosis [31] and enhancing the bactericidal activity of macrophage-lineage cells in zebrafish [32]. During infection with the Zika virus, itaconate was found to alter the neuronal metabolism to suppress viral replication [33], indicating that its modulatory effects are not restricted to myeloid cells. The direct antimicrobial functions of itaconate are thought to rely largely on the inhibition of isocitrate lyase, an enzyme of the glyoxylate shunt that is essential for growth under glucose-poor conditions, and that is required for the virulence of several pathogens, including C. albicans [31, 34, 35]. In contrast, bacteria often harbor genes involved in itaconate degradation, allowing them to counter the inhibitory mechanisms deployed by itaconate and survive inside the host [36]. Moreover, pathogens such as Staphylococcus aureus and Pseudomonas aeruginosa were recently shown to adapt to itaconate-rich environments and use this metabolite as a carbon source for the production of biofilms, contributing to the establishment and progression of infection [37, 38]. The therapeutic administration of inhaled itaconate has been shown to improve pulmonary fibrosis in mice [39], a disease that often develops due to exposure to airborne fungi [40] and that, in turn, further potentiates the development of respiratory fungal infections [41]. Whether itaconate plays a role in the immune response to fungal pathogens other than C. albicans remains to be explored, although the metabolism of acetate, a carbon source metabolized also through the glyoxylate shunt, impacts virulence traits and the pathogenicity of A. fumigatus [42]

In response to inflammatory stimuli, macrophages accumulate succinate that, in turn, acts as a proinflammatory redox signal to the transcription factor HIF-1α and the production of IL-1β [43]. Succinate oxidation also potentiates the generation of mitochondrial ROS [44], which represent critical effectors required for antifungal immunity [45]. Indeed, the balance between the production of ROS and reactive nitrogen species by the host and the fungal stress response is a key feature of the host-fungus interaction [46]. The production of nitric oxide (NO) is modulated by the metabolism of amino
acids, which also plays an important role in macrophage polarization [47]. In this regard, C. albicans was shown to upregulate arginase activity and limit NO production in macrophages via chitin-mediated signals, skewing macrophage polarization towards an anti-inflammatory profile which ultimately restrains antimicrobial functions and mediates fungal survival [48]. In contrast, granulocyte-mediated clearance of A. fumigatus occurred independently of arginine availability [49], a finding that supports distinct pathogen-driven metabolic strategies to subvert antifungal immune responses.

The catabolism of tryptophan via the activity of indoleamine-2,3-dioxygenase 1 (IDO1) also represents an essential mechanism in the modulation of antifungal immunity [50]. IDO1 acts as a physiological checkpoint that controls immune homeostasis through its downstream catabolites – referred to as kynurenines – and provides the host with adequate protective immune mechanisms [51]. In particular, IDO1 activity induces differentiation of T regulatory cells, while inhibiting the development of T helper 17 cells, thus playing a central role in cell lineage commitment across experimental fungal infections in the context of detrimental inflammation, including chronic granulomatous disease and cystic fibrosis [52, 53]. The airway expression of IDO1 was also found to inhibit pathogenic T cells in response to fungal antigens [54], a finding consistent with the requirement for IDO1 activity in the non-hematopoietic cell compartment for protective tolerance against A. fumigatus [55]. Tryptophan-derived metabolites may also be produced through the activity of bacterial communities in the intestinal microbiota, which establishes a highly tolerant immunological microenvironment allowing the commensalism of C. albicans in the gut [56]. Of note, IDO1 activity was found to be required to inhibit the yeast-to-hyphae transition of C. albicans [57].

The expression and function of IDO1 are influenced by common human genetic variation [58]. Accordingly, single nucleotide polymorphisms in IDO1 that impair its expression were found to influence the risk of developing recurrent vulvovaginal candidiasis [59], as well as aspergillosis in patients with cystic fibrosis and recipients of allogeneic hematopoietic stem-cell transplantation [60]. Remarkably, A. fumigatus was recently found to harbor genes encoding fungal IDO1-like enzymes and their deletion resulted in increased virulence in a mouse model of aspergillosis [61], thus highlighting the crucial role of the interplay between fungal and host tryptophan metabolic routes in shaping host-fungus interactions. Collectively, the bulk of available data suggests that drugs capable of potentiating IDO1 expression and activity may represent valuable therapeutic tools and that IDO1-
based immunotherapeutics could be more effective if tailored to the genetic profile of individual patients [62].

**Trained immunity as a therapeutic strategy to rescue immune impairments**

A growing body of evidence has revealed alterations of the innate immune system that potentiate responses and ultimately generate characteristics of memory [63]. Trained immunity, a *de facto* innate immune memory, allows for a long-lasting and broad-spectrum resistance to pathogens. In this context, macrophage exposure to the vaccine Bacillus Calmette-Guérin (BCG), fungal β-glucan, or oxidized low-density lipoprotein enhanced effector functions toward subsequent heterologous stimuli, while it conferred protection against secondary lethal infections in mouse models, namely by *C. albicans* [64-66].

Trained cells harbor altered metabolic programs that sustain the rewiring of the epigenetic landscape and allow for enhanced immune effector functions. Trained macrophages rely on a highly energetic metabolism characterized by enhanced glycolysis, TCA cycle, and oxidative phosphorylation [64]. In accordance, the mTOR/HIF-1α axis was demonstrated to mediate the metabolic and functional reprogramming of β-glucan-trained macrophages [12]. Cholesterol biosynthesis is also a central pathway for trained immunity as shown by its induction by the intermediate mevalonate [67]. Trained immunity is also conferred by the epigenetic and metabolic reprogramming of hematopoietic stem cells and their skewing towards myelopoiesis [68, 69]. The broad clinical relevance of this molecular process was emphasized in a recent randomized clinical trial that showed that BCG vaccination of elderly individuals decreased the incidence of new respiratory infections [70]. The induction of trained immunity thus represents an interesting tool to harness the potential of innate immunity in patients with immune impairments (Figure 2). However, increasing immune responses may be particularly challenging in selected pathologies. Not only can immune cells be epigenetically encoded to dampen responses to inflammatory stimuli, but also the decreased number of circulating immune cells might not be sufficient even if their activity is potentiated.
In patients under intensive care, fungal infections often give rise to sepsis, which involves the hyperactivation of the immune system followed by tolerance or immune paralysis. Immune paralysis also comprehends epigenetic and metabolic changes [71] but, in contrast to trained immunity programs, these changes ultimately increase the susceptibility to secondary infections [72, 73]. Exposure to β-glucan restored the responsive phenotype of human monocytes tolerized with LPS, a finding that was confirmed in a human endotoxemia model [74]. The integrity of the TCA cycle in LPS-stimulated macrophages was maintained by β-glucan through the inhibition of IRG1 expression [75]. Of note, while the anti-inflammatory properties of itaconate make it an interesting target for the reversal of immune paralysis, at the same time, itaconate may also represent a valuable therapeutic tool to decrease detrimental and exacerbated antifungal immune responses.

Another functional feature of patients with sepsis regards the defective activation of LC3-associated phagocytosis (LAP), a non-canonical autophagy pathway that plays a non-redundant role in the resistance to infection with A. fumigatus [76-78]. Recently, monocytes from patients with sepsis were found to display a defective activation of LAP, which was reversed by the administration of recombinant IL-6 [79]. It is thus tempting to consider the modulation of LAP as a promising immunotherapeutic intervention in sepsis, particularly given the ability of β-glucan to increase the expression of Rubicon [80], a critical effector molecule of LAP. The induction of trained immunity could thus also represent a promising avenue for the treatment of fungal sepsis.

Several trained immunity inducers are already under clinical use. For example, muramyl tripeptide is employed in the treatment of osteosarcoma and BCG is in clinical use for bladder cancer [81]. Notably, trained immunity was found to be elicited by dimethyl fumarate [82], a drug currently under use for the management of multiple sclerosis [83]. Also approved for human use is the vaccine adjuvant and TLR4 agonist monophosphoryl lipid A (MPLA). MPLA has been shown to not only improve resistance to several pathogens, including C. albicans [84] but also to induce the metabolic rewiring of macrophages characterized by a sustained increase in glycolysis and oxidative phosphorylation [84] in a similar manner to other inducers of trained immunity. Collectively, these molecules represent attractive candidates for repurposing toward the induction of trained immunity in immunocompromised patients.
Targeting metabolic homeostasis at the host-fungus interface

During infection, the host and the pathogen compete for limiting levels of nutrients, such as glucose. It is thus not surprising that a glucose-rich diet has been found to improve the survival of mice in a model of disseminated candidiasis [16]. Importantly, induction of trained immunity may also prevent macrophage death due to glucose starvation. Trained macrophages not only present increased glycolysis but also display increased oxidative phosphorylation, and thus trained cells might not be committed to glycolysis for energy production. A benefit of the enhanced glucose uptake is also envisaged in uremic individuals, who exhibit a hyperinflammatory state and are at increased risk of developing fungal infections. Uremia downregulates the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/AKT pathway, causing hyperactivation of the glycogen synthase kinase 3β (GSK3β) and thus inhibiting glucose uptake [85]. Accordingly, the pharmacological blockade of GSK3β using the specific inhibitor SB415286 or lithium chloride restored glucose uptake, but also ROS production and the candidacidal activity of neutrophils, in a mouse model of kidney disease with systemic fungal infection. The preclinical efficacy of GSK3β inhibition was confirmed by the rescue of the fungal killing capacity in neutrophils isolated from hemodialysis patients. Nutritional supplementation was also protective against influenza infection and viral sepsis, but it was instead detrimental in bacterial sepsis by *Listeria monocytogenes* [86]. Therefore, although favoring glucose metabolism may represent a promising therapeutic possibility, the opposing effects of fasting metabolism on different infections suggest its utility on a pathogen-dependent basis.

Exacerbated immune responses to infection may also drive fungal sepsis. In this scenario, it might be advantageous to combine antifungal agents with inhibitors of glucose uptake and glycolysis to ultimately decrease inflammation. In this regard, the glucose analog 2-deoxy-D-glucose (2-DG) that blocks glucose metabolism was found to decrease cytokine production in mouse models of infection with *C. albicans* [13] and *A. fumigatus* [17]. Moreover, metformin, a widely used drug in the treatment of type 2 diabetes as a glucose-lowering agent, which activates the AMP kinase and inhibits mTOR, or the mTOR blockade itself, decreased cytokine production and survival in experimental disseminated candidiasis [13, 16]. Other inhibitors of glucose uptake or glycolysis, such as the HIV-protease inhibitor ritonavir [87], the pyruvate dehydrogenase kinase inhibitor dichloroacetate [88], and
the small-molecule competitive lactate dehydrogenase inhibitor FX11 [89] might also be of future interest in the context of fungal infections.

The rewiring of metabolic pathways may consume or compartmentalize metabolites, restricting pathogen access to nutrients, as depicted for glucose accessibility during infection. Interestingly, the pulmonary niche was found to impose a decreased responsiveness of alveolar macrophages, by impairing glycolysis and promoting pathways of lipid metabolism [90]. These findings highlight the crucial role of the tissue milieu for both immune responses and the virulence of pathogens, including fungi. Moreover, the metabolic profiles differ at different tissues, providing substrates that regulate not only fungal fitness, but also immune cell function and their interaction. Another example of compartmentalization derives from anemia of inflammation, which arises due to infections or autoimmune disorders that promote a proinflammatory state [91]. Host and invading pathogens compete for iron availability, as it is an essential co-factor for several proteins relevant for a myriad of processes, such as DNA replication and mitochondrial function. Iron is especially relevant for highly proliferative cells, and lack of iron blunts T and B cell responses [92]. Systemic immune activation of the host induces changes in iron intestinal absorption, trafficking, and cellular retention, thus decreasing iron availability to pathogens. To counter this, fungi produce siderophores that capture iron from host iron-binding proteins in human serum, while restricting iron access to host immune cells and modulating their activity [93]. Accordingly, elevated circulating iron levels have been associated with an increased risk of systemic fungal infection in hematological patients [94]. Moreover, the iron chelator deferiprone was shown to decrease fungal burden in a mouse model of cornea infection by *A. fumigatus* [95] and improve survival of mice infected with the mucormycete *Rhizopus oryzae* [96]. Ciclopirox, a potent topical antifungal agent, exerts its effects partly by chelating polyvalent metal cations such as iron [97]. Inhibition of fungal iron uptake, namely via targeted iron chelation therapies, represents thus an interesting therapeutic strategy.

Iron is not only a limiting nutrient for pathogen virulence [98, 99], but it also plays a regulatory role in host immune responses [100]. For example, iron-loaded macrophages exhibited a proinflammatory phenotype in diverse disease contexts, such as spinal cord injury [101], multiple sclerosis [102], and cancer [103]. On the other hand, acute iron chelation promotes an anti-inflammatory shift, as seen by the decrease in LPS-induced cytokine production by human
macrophages [104]. This acute iron deprivation also enhanced glycolysis and lipid droplet formation while it downregulated oxidative phosphorylation, possibly due to the disruption of the iron-containing complex II of the respiratory chain. Interestingly, labile heme induces a trained immunity program that confers protection against LPS-induced sepsis in mice [105]. Thus, the targeted modulation of iron accessibility, be it by iron chelation when a proinflammatory phenotype is maladaptive, or by the delivery of iron in nanoparticles or heme to promote inflammation [106] is an attractive avenue to tailor immune metabolism and function.

Concluding remarks

The goal of host-direct approaches targeting immunometabolism is ultimately the exploitation of intrinsic metabolic pathways in the treatment of disease, including fungal infections. The targeting of host metabolism instead of fungal traits would decrease selective pressure and consequently diminish the development of unwanted resistance to antifungals. Selected metabolic pathways may be harnessed to potentiate immune responses or dampen them when they become maladaptive, while considering the pathogen involved, the affected tissue, and the disease state. Importantly, a rational strategy to identify and interpret immunometabolic signatures of susceptibility to fungal infection through the immune profiling by multi-omics approaches, including genomics, metabolomics, and epigenomics, holds the promise to identify patients at high-risk of infection that would benefit the most from targeted preventative measures. To achieve this goal, further studies are needed to better understand the pathogenesis of fungal diseases, their progression profile in time and space, and the host-fungus interplay in the context of effector immune cells. The exploitation of new approaches to study the diverse metabolic programs of specific cells, tissues, and diseased states is ultimately necessary to pave the way toward the effective clinical modulation of immunometabolism in the field of fungal disease.
Data Availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Competing interests

The authors declare no competing interests.

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Author contributions

Conception: SMG, AVF, CC and AC. Preparation of figures: SMG and AVF. Writing and literature review: SMG and AVF. Critical revision of the article: CC and AC. All authors have read, edited, and approved the final version of the article.
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Figure Legends

Figure 1. Metabolic reprogramming of myeloid cells in response to fungal infection. Recognition of fungal pathogens by pathogen recognition receptors (PRRs) is accompanied by the upregulation of glycolysis and production of lactate. In these conditions, the TCA cycle and oxidative phosphorylation (OxPhos) are often repressed, resulting in the accumulation of intermediates such as succinate and itaconate, and enhancing the generation of reactive oxygen and nitrogen species. In response to *C. albicans*, the activation of glycolysis is triggered by the recognition of β-glucan by dectin-1, a process that can be in turn exploited by the fungus through its ability to compete for glucose and ultimately promote macrophage death. Sensing of lactate secreted by immune cells also drives the masking of β-glucans in the fungal cell wall and immune evasion. The activation of glycolysis during infection with *A. fumigatus* is instead triggered by the release of melanin during germination. By sequestering calcium within the phagosome, melanin promotes the recruitment of mTOR which, in turn, mediates the activation of downstream metabolic genes and regulators. The catabolism of tryptophan (Trp) by the indoleamine-2,3-dioxygenase 1 (IDO1) enzyme also regulates antifungal immune responses and controls fungal morphology through its downstream catabolites, collectively referred to as kynurenines (Kyn).

Figure 2. Trained immunity as a tool to potentiate host defense. Microbial or endogenous stimuli activate innate immune cells. Depending on the dose or stimuli, innate immune function may be increased when encountering a secondary stimulation (trained immunity) or cells may become unresponsive or anti-inflammatory (tolerance). Trained immunity confers long-term protection thought the myelopoietic skewing of hematopoietic stem cells, giving rise to monocytes with enhanced effector functions. They rely on metabolic changes, such as increased glycolysis and OxPhos, which supports epigenetic rewiring that promotes the expression of proinflammatory genes culminating in the increased secretion of cytokines. Thus, trained immunity inducers may be an attractive therapeutic tool to revert tolerance, possibly rescuing states of immune paralysis in sepsis and decreasing the risk of secondary infections.