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The Immunometabolism Respiratory Infections: Disintegration of Microbial-Immune-Metabolism Crosstalk Regulates Disease Progression

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العدوى التنفسية المناعية الايضية: تفكك التفاعل المناعي الايضي الميكروبي ينظم تطور المرض

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Abstract
Respiratory infections caused by influenza, respiratory syncytial virus (RSV), transmission of the viruses that cause the current pandemic and transmission of the bacteria Mycobacterium tuberculosis, represent a major health burden globally. Beyond direct pathogen--host interactions, there is mounting evidence that the metabolic programming of immune and structural lung cells--immunometabolism--critically affects outcome of infection. Pathogens then take over or alter metabolic pathways to their advantage for replication and immune cells then rewire metabolism to their advantage against infection, a dynamic metabolic battlefield. This review summarizes the latest progress in immunometabolism from respiratory infections in terms of metabolic-immune-microbial crosstalk, severity of disease, and novel host-directed therapeutic targets. Pathogenic: Across pathogens, infection triggers glycolytic rewiring, tricarboxylic acid (TCA) cycle remodelling, deregulation of lipid and amino acid metabolism metabolic hubs (itaconate/IRG1, succinate/HIF-1a and NAD+/sirtuin axes) are linked to the metabolic flux, cytokine production, ROS signalling and tissue injury. Human metabolomic research presents disease severity fingerprints including lactate, succinate, kynurenine and ceramide pathways. Therapeutically, metabolic interventions (glycolysis inhibitors, itaconate derivatives, NAD+ boosters) hold promise in preclinical models, although only limited clinical translation has been made. Immunometabolic reprogramming: Immunometabolic reprogramming is a determinate of respiratory infection pathogenesis and resolution. Targeting metabolic checkpoints could be a new field for host-directed therapy for emerging treatments, but requires context-specific approaches, combination of spatial-multi-omics, endotyping metabolomics in clinical trials.

Keywords: immunometabolism, respiratory infections, glycolysis, itaconate, HIF-1- a, metabolomics, host directed therapy.

الملخص
تمثل العدوى التنفسية الناتجة عن فيروس الإنفلونزا، والفيروس الاخلوي التنفسي (RSV)، وانتقال الفيروسات المسببة للجائحة الحالية، إضافةً إلى انتقال بكتيريا المتفطرة السلية (Mycobacterium tuberculosis)، عبئًا صحيًا كبيرًا على مستوى العالم. وإلى جانب التفاعلات المباشرة بين الممرض والمضيف، تتزايد الأدلة على أن البرمجة الأيضية للخلايا المناعية والهيكلية للرئة - الأيض المناعي_ تؤثر بشكل حاسم على نتيجة العدوى ثم تستولي الممرضات على المسارات

الأيضية أو تُغيّرها لصالحها من اجل تكاثرها، بينما تقوم الخلايا المناعية بعد ذلك بإعادة توجيه أيضها لمواجهة العدوى، في ما يشبه ساحة معركة أيضية ديناميكية. يستعرض هذا المقال آخر التطورات في مجال الأيض المناعي في العدوى التنفسية من حيث التفاعل بين الأيض والمناعة والميكروبات، وشدة المرض، والأهداف العلاجية الجديدة الموجهة نحو المضيف.مسببات الأمراض: في مختلف مسببات الأمراض، تُحفز العدوى إعادة برمجة مسار تحلل الجلوكوز، وإعادة تشكيل دورة حمض الستريك (دورة كريبس)، واضطراب استقلاب الدهون والأحماض الأمينية. ترتبط المحاور الأيضية الرئيسية (إيتاكونات/IRG1، وساكسينات/HIF-1α، وNAD+/سيرتوين) بالتدفق الأيضي، وإنتاج السيتوكينات، وإشارات أنواع الأكسجين التفاعلية، وتلف الأنسجة. تُقدم أبحاث الأيض البشري بصمات شدة المرض، بما في ذلك مسارات اللاكتات، والساكسينات، والكينورينين، والسيراميد. علاجيًا، تُبشر التدخلات الأيضية (مثبطات تحلل الجلوكوز، ومشتقات الإيتاكونات، ومعززات NAD+) بنتائج واعدة في النماذج ما قبل السريرية، على الرغم من أن تطبيقها السريري لا يزال محدودًا. إعادة برمجة المناعة الأيضية: تُعد إعادة برمجة المناعة الأيضية عاملًا حاسمًا في نشأة عدوى الجهاز التنفسي وشفائها. قد يكون استهداف نقاط التفتيش الأيضية مجالًا جديدًا للعلاج الموجه للمضيف من أجل العلاجات الناشئة، ولكنه يتطلب مناهج خاصة بالسياق، ومزيجًا من علم الجينوم المكاني المتعدد، وعلم الأيض الداخلي في التجارب السريرية.

الكلمات المفتاحية: المناعة الأيضية، التهابات الجهاز التنفسي، تحلل الجلوكوز، إيتاكونات، HIF-1-α، علم الأيض، العلاج الموجه للمضيف.

Introduction

Respiratory infections are among the leading causes of morbidity and mortality even now in our world. In the last few years, it has become evident that pathogen load or by classical immune responses are not the only factors that determine the course of infection; interactions between pathogen and host metabolism have also been implicated. In particular, there has been the rise of immunometabolism - where metabolic pathways interact with function of immune cells - as a determinant in influencing disease progression in the lung. Enzymatic rewiring in cellular compartments of the immune and structural lung (i.e., macrophages, epithelial cells, neutrophils, T cells) can affect viral replication, inflammatory cytokines, damage to tissue and recovery. The primary paradigm is that activated immune cells tend to switch from oxidative phosphorylation to aerobic glycolysis ("Warburg effect") in order to supply the drastic needs for biosynthesis and effector function. Hypoxia-inducible factor 1 alpha (HIF-1a) is a master regulator of this metabolic switch inducing the genes encoding the glycolytic (pyruvate metabolism) enzymes and glucose facilitators and is stabilized by metabolites like succinate (prolyl hydroxylase inhibitors) (Corcoran & Taylor, 2016). Macrophages (M) are cells that can be activated by HIF-1a-mediated stabilization and the development of IL-1v when they are stimulated in a pro-inflammatory way. At the same time, metabolites that are a product of the tricarboxylic acid (TCA) cycle, such as succinate and itaconate, are immunometabolites - metabolites that not only work as metabolic intermediates but also act as signaling molecules. Succinate accumulation will promote inflammation even further by means of reactive oxygen species (ROS) generation and HIF-1a activation (Palsson-McDemott, 2025). In contrast, the other product, itaconate (made by ACOD1/IRG1 from cis-aconitate), can often act as a negative feedback regulator: it can inhibit the succinate dehydrogenase (SDH); activate the Nrf2 and ATF3 pathways; and inhibit the activation of the NLRP3 inflammasome (Lang et al., 2024). Whereas immunometabolism has been intensely explored within the setting of sepsis or cancer models, the relevance of immunometabolism to respiratory infections (influenza, RSV, SARS-CoV-2, *Mycobacterium tuberculosis*) is still being characterized. Immune system pathogens can also actively modulate host metabolism; *Mycobacterium tuberculosis* is known to upregulate glycolysis via HIF-1a induction in macrophages and modulate sirtuin expression to fine-tune NFkB signaling (Dos Reis *et al*., 2023). The lung environment, in which oxygen and nutrient gradients, surfactant lipids and local microbiota shape the pulmonary environment, results in a complex metabolic niche, in which metabolic crosstalk between pathogen and immune and epithelial compartments can have critical importance for determining metabolic outcomes (Hu *et al*., 2024). The immunometabolism of respiratory infections is not only linked to an understanding of the mechanism involved in infection, but can actually be transformed into concrete clinical applications. Metabolic fingerprints such as elevated lactate, build-up of succinate, various kynurenine/tryptophan, and lipid dysregulation are becoming good biomarkers of the severity of the disease, progression to ARDS, and chances of mortality. These signatures can aid in early risk stratification, therapeutic response monitoring and prediction of long-term complications such as post-viral syndromes and so forth. From the point of view of lateral movement, the targeting of immunometabolic pathways represents a new approach for precision medicine. Interventions like glycolysis inhibitors (2-DG), itaconate dervatives, NAD+ boosters, and repurposed drugs such as metformin or fumarates are promising new candidates as adjuvant therapies that would complement antivirals and immunomodulators. By using metabolomic profiling in clinical decision-making, it is possible that clinicians will be able to personalise their treatments based on the metabolic endotypes of their patients, ultimately leading to improved clinical outcomes and less immunopathology (Dos Reis *et al*., 2023).

In this review, it aims to integrate recent mechanistic and translational studies on immunometabolism in respiratory infections, they pay attention to metabolism nodes (glycolysis, TCA cycle intermediates including itaconate), integrate some human metabolomic data and suggest metabolic interventions as host-directed therapies.

2. Cell metabolism of the lung and immune system in homeostasis

The lung environment is metabolically limited and is structurally distinct: the alveolar space is relatively hypoxic, the air-liquid interface is rich in surfactant lipids and nutrient diffusion is restricted by the thin alveolar epithelial-barrier, and by the restricted vascular surface exposure to luminal surfaces. Immune populations in the lung (in particular, resident macrophages) are therefore compelled to develop metabolism programs adapted to these limitations. Instead of representing a passive homeostasis, lung immunometabolic homeostasis is a poised state that may be dynamically reconfigured upon perturbation. Alveolar macrophages (AMs), which are embedded into the low oxygen-alveolar fluid containing surfactant and low nutrients, are known to be generally dependent on oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) in mitochondria during homeostasis. It is this metabolic signature that underlies their anti-inflammatory activity, ability to efficiently clear debris, and ability to limit excess activation. Indeed, compared to recruited macrophage populations, AMs at steady state have a decreased glycolytic flux, increased mitochondrial respiration, as well as expression of lipid metabolic regulators (e.g., PPARg) responsible for catabolizing lipids from surfactant (Andrews *et al*., 2022; Wculek *et al*., 2022). For instance, AMs perform excessive degrees of PPARy, a transcriptional regulator of lipid uptake and oxidation programs. (Andrews *et al*., 2022), there is evidence of the heterogeneity of lung macrophages: interstitial macrophages (IMs) and monocyte-derived macrophages in the interstitial tissue are in closer contact with vasculature so have more access to substrates. Furthermore, those cells have a high component metabolic plasticity and are able to dynamically switch between glycolysis and oxidative metabolism in response to signals and regional nutrient status (Wculek *et al*., 2022). A recent mini-review recalls the specificity of the glycolytic metabolism of tissue-resident alveolar macrophages in comparison with the recruited lung macrophages and demonstrates how: (i) in AMs the glycolytic programme is kept small under steady state but (ii) it can be quickly upregulated in recruited groups (Woods & Mutlu, 2025). Also, it is previously recognized that neutrophils from the lung tissue have more complex metabolism than do their counterparts with in vivo counterparts. Although once thought to be very glycolytic, hepatocytes more recently have been shown to undergo mitochondrial metabolism with important functions such as chemotaxy, reactive oxygen species (ROS) modulation and NETosis, particularly during stress/inflammation (Maldarelli & Noto, 2024). Main pulmonary epithelial cells (human alveolar type II and type I cells) and lung resident lymphocytes are metabolically poised by basal levels of mitochondrial respiration with low rates of glycolysis and the metabolic plasticity required for adequate anabolic and/or glycolytic metabolism in response to activation/injury. For example, in a recent study, mitochondrial long-chain fatty acid oxidation (mtLCFAO) in alveolar epithelial type II (AT2) cells is involved in the regulation of alveolar immune responses, and Henrique da Silva's group showed that downregulation of mtLCFAO in alveolar epithelial type II (AT2) cells had an anti-inflammatory effect on neutrophilic lung inflammation in lung injury models (Chung *et al*., 2024). Taken together, these data highlight that lung epithelial cell metabolism is central to lung immune-homeostasis and cross-talk and that immunometabolism in the lung is a state of simple homeostasis and of flexibility and adaptation at baseline. Such a lipid-rich and nutrient-limited microenvironment defines a constrained metabolic state in tissue-resident immune and structural cells; this uniferous status is being primed for profound re-programming in response to pathogen invasion. In doing so, metabolic rewiring does not just become a defensive tool but may become the location of pathology at the time of transition.

3. Pathogen Mediated Metabolic Reprogramming

3.1 Influenza A

Influenza A infection is followed by rapid profound metabolic alteration of host cells including macrophages and epithelial cells. This cell type provided that first viral entry and host detection via pattern recognition receptors (TLRs, RIG-I) lead to signaling cascades, containing PI3K/AKT, mTOR, and NF-kB. These node towards sporadic stabilization of HIF-1a. Stabilised HIF-1a induced up-regulation of transcription of the glycolytic enzymes including hexokinase 2 (HK2) and 6-phosphofructo-2-kinase (PFKFB3), boosted the expression of glucose transporter, and augment lactate production - thus enforcing a glycolytic reprogramming (Zhang *et al*., 2024). This metabolic programming facilitates the rapid production of ATP and provision of biosynthetic precursors required for cytokine synthesis (e.g. IL-1beta, TNF, IL-6) and antiviral effector responses. Demonstrations of simultaneous rewiring or truncation of parts of the tricarboxylic acid (TCA) cycle in particular, effector pathways downstream blocks, or metabolic derangements rate-limiting for succinate dehydrogenase can promote the accumulation of succinate which stabilizes HIF-1a by down-regulating prolyl hydroxylases and thus allowing creating positive feedback between glycolysis and inflammatory signaling. Excess succinate can also enhance the production of reactive oxygen species (ROS) and can synergistically enhance NF-kB-mediated

transcriptional responses. In murine models of severe influenza pneumonia, this metabolic reprogramming is associated with lung injury and alveolar damage and edema, suggesting that unchecked glycolysis can drive immunopathology (Ma *et al*., 2024). Importantly, the timing and extent of activation of glycolysis plays an important role. The early glycolysis maintains immune activation and containment of pathogens, while sustained dominance of glycolysis could communicate impairment of the resolution, inadequate tissue repair or even promote lung damage. Thus, while the completion of glycolytic reprogramming is important for mounting an effective immune response, the regulation of this process will have to be tightly controlled to avoid collateral injury.

3.2 SARS-CoV-2

SARS-CoV-2 Remodel Host Metabolism Potently in both Epithelial and Immune Compartments. Infected airway epithelial cells are characterized by increased uptake of glucose, lactate production and axonal expression of the pentose phosphate pathway (PPP) used for the production of the reducing agent (reduced) nicotinic acid diphosphate (NADp) - which is favorable to the synthesis of viral RNA (redox support). Pharmacologic inhibition of glycolysis using 2-deoxy-D-glucose (2-DG) decreases replication of the main causative agent of the respiratory syndrome, namely, infection by the bacterium with the current name of Coronavirus (commonly referred to as Covid-19) and this in cellular systems the infective capacity of progeny virus by weakening the infectious power of virions formed by viral RNA (Bojkova *et al*., 2020; Bhatt *et al*., 2022). Beyond the metabolism of carbohydrates, the virus modifies pathways of lipids: it turns on proteins called SREBP and induces the biogenesis of lipid droplets such as DGAT: these enzymes support the assembly and egress of the viruses (Soares *et al*, 2023; Yuan *et al*, 2021). Sphingolipid signalling involved in cellular entry Acid sphingomyelinase 2 meddles in uptake of the novel coronavirus by epithelial cells of the respiratory tract (Carpinteiro *et al.* 2020; Carpinteiro *et al*., 2021). In the immune system, exposure to the difficult to control coronavirus results in the stabilization of hypoxia-inducible factor 1 alpha, or HIF-1 a driving a pro-inflammatory (glycolysis-dominant) program the severity of which is increased by hyperglycemia, leading to impaired interferon signaling in T cells and reduced epithelial viability (Codo *et al*., 2020). Persisting metabolic disturbances can be found months following acute infection (Saito *et al*., 2025). Importantly, targeting immunometabolic check points is of translational value. The immunometabolite-derived NRF2 agonist 4-octyl-itaconate (4-OI) and an approved drug (dimethyl fumarate DMF) limit the replication of the virus and improve virus-associated inflammation in experimental models and prophylactic/therapeutic administration of itaconate has been reported to reduce disease-associated injuries caused by infection with the coronavirus in vivo (Olagnier *et al*., 2023; Jiang *et al*., 2025).

3.3 Respiratory Syncytial Virus (RSV)

RSV is a leading cause of respiratory disease, particularly among infants and elderly persons. Unlike influenza or more recently with the coronavirus (SARsCoV2), re-infection with the RSV virus is rather common, and indicates less overt strategies of immune evasion such as metabolic modulation. The RSV G protein is implicated in the host medical condition changes of host transcriptomic and probably metabolic control, resulting in inhibition of antiviral reactions and preference for pathology of lungs (Anderson *et al*., 2024). In fact, RSV has been identified to co-opt hypoxia-inducible factor-1a (HIF-1a) in order to increase glycolysis and reprogram host metabolism (Chen *et al*., 2023). Although there is still a lack of explicit isotope tracer studies, the accumulating evidence suggests that the leading mechanism by which RSV infection causes increased glycolysis and activation of the pentose phosphate pathway (PPP) in airway epithelial and innate immune cells within the context of viral infection satisfies both antiviral energy needs and redox homeostasis (Flores-Torres *et al*., 2025). The energetic cost of cytokine and interferon production under the pressure of energetic resource limitation may necessitate competition between metabolic and immune functions. Depending on whether glycolytic capacity is exceeded or mitochondrial stress occurs, maladaptive immunopathology may be the result. In support of metabolic heterogeneity, unique transcriptomic immune endotypes found in RSV patients are associated with disease severity with an implication that underlying metabolic differences predispose to more severe disease (Camps *et al*., 2025). In support of metabolic heterogeneity, distinct transcriptomic immune endotypes found in RSV patients is associated to disease severity with an implication that underlying metabolic difference predisposes to worse disease. Because metabolic rewiring in RSV is relatively uncharacterized, future studies using isotope tracing, single cell metabolomics, and targeted metabolic perturbations are important to understand how RSV manipulates host immunometabolism, and whether host-directed metabolic therapies can lead to better clinical outcomes.

3.4 passages of *M. tuberculosis* were represented.

M. tuberculosis has no other niche than macrophages and manipulates a long-term interaction with hosts' immunometabolism. Early during infection, macrophages undergo a glycolytic "burst" to support antimicrobial effector functions (reactive oxygen species [ROS]; nitric oxide [NO]; cytokine production) while suppressing oxidative phosphorylation (OXPHOS) and mitochondrial anabolic pathways (Howard *et al.*, 2020). Over time, however, metabolic adaptation develops: oxidative metabolism may be re-engaged by macrophage cells whereas

they may increase mitochondrial fitness and switch to fatty acid oxidation (FAO) and lipid oxidation, especially in granulomatous hypoxic areas (Chandra *et al*., 2022; van der Klugt *et al*., 2025). Hyper-nitric oxide generation through inducible nitric oxide synthase (iNOS) is able to directly suppress mitochondrial electron transport treecomplements, increasing ROS as well as metabolic stress, and shifting this cell towards compensative glycolysis (Park *et al*., 2021). Interestingly, *M. tuberculosis* alters host lipid droplets and cholesterol metabolism in order to sustain infection, as well as TCA intermediates (e.g., citrate, malate) to support host lipid metabolism. Notably, the ESAT-6 or other secreted effectors may increase the host glucose uptake and lipogenesis, and divert the host metabolic flux in the direction of the benefit for the pathogen (Chandra *et al*., 2022; Costa *et al*., 2023). Indeed, provision of M. tuberculosis-inducible lipid storage remodeling of host lipid droplets within infected macrophages adds further credence to the idea that the bacterial pathogen manipulates the lipid storage environment within host lung alveoli to support its intracellular niche (Costa *et al*., 2023). Transcriptomic profiling in human tuberculosis cohorts also strengthens the immunometabolic story: Increased expression of immune-related genes IRG1/ACOD1, genes of the hypoxia-induced factor (HIF) pathway and lipid metabolism regulators were linked to disease activity, disease burden with bacteria and risk of disease progression (Chandra *et al*., 2022; Kilinç *et al*., 2021). Thus, in steady-state infection, the system involves a metabolic tug-of-war: host cells try to reprogram for anti-microbe functions, the pathogen reprograms as well and the metabolic balance generated is possibly the crucial factor dynamically linking containment, pathology or reactivation.

4. Microbes in Relation to Immune System Metabolic Nodes relevant to the Crosstalk

thay found the landscape of pathogen-induced metabolic reprogramming to be cellular and to be complex. Yet, these pathways look quite similar across infection contexts: nodes of convergence between flux of substrates and immune signaling are prevalent. These nuclei serve as metabolic switches to immune fate decisions resulting in changes in inflammation, antimicrobial activity and immune tolerance. Below, they discuss five such hubs within the context of respiratory infection.

4.1 Itaconate / IRG1 / ACOD1 Axis

IRG1 (also termed ACOD1) encodes an enzyme that catalyzes the conversion of cis-aconitate to itaconate, a TA cyclotron (TCA) derived immunometabolic, with signaling capabilities. Itaconate suppresses succinate dehydrogenase (SDH) which limits the accumulation of succinate and the production of ROS. It also alkylates and inhibits KEAP1 such that NRF2 is quadratically activated and curbs NLRP3 inflammasome activity by inducing ATF3 (Mills *et al*., 2015). The impact of itaconate in tissue resident alveolar macrophages may be more complex than previously known. A new study by Shan *et al*., (2025) has shown that endogenous itaconate actually enhances NLRP3 activation and proinflammatory cytokine secretion in alveolar macrophages that worsen lung injury in vivo. In direct contrast, other derivatives like dimethyl itaconate (DI) and 4-octyl itaconate (4-OI) inhibited inflammation by such macrophages, confirming the importance of chemical species, as well as the cellular environment. These studies conclude that the transposition of itaconate into therapeutic approaches must take into account an elaborate focus on dosage, by-products, tissue type, and the environment. In lung infection-alveolar macrophages, in particular, are often placed in conditions of surfactant/nutrient deprivation-and the balance may be proclined toward pathological inflammation as opposed to protection.

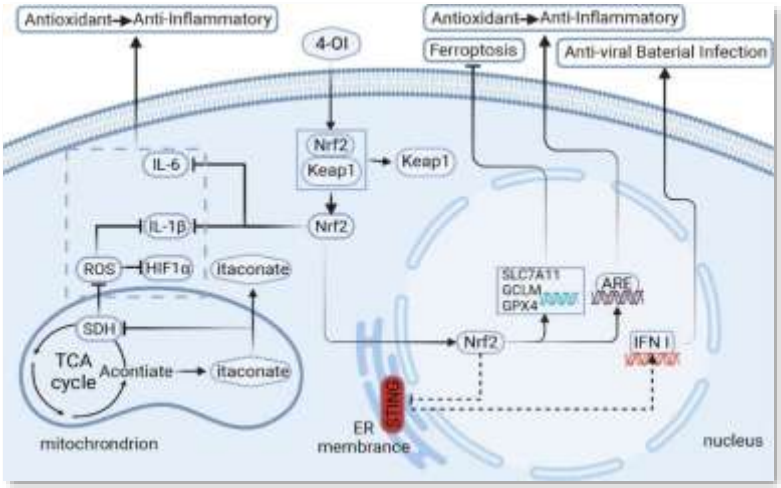

Figure 1: Reaginated metabolic regulation of immunological reproduction on itaconate and a derivative of itaconate, 4-octyl itaconate (4-OI) Itaconate a product of TCA cycle from cis-aconitate also suppresses SDH and suppresses ROS production, while 4-OI drives Nrf2-Keap1 pathway activation, which induces antioxidant and anti-inflammatory effects. Other effects include a block in STING-mediated IFN-I signaling and modulation of ferroptosis, thus propagating the concept of metabolic rewiring as host protection during respiratory infections.

4.2 Succinate / HIF-1α Axis

Enhancement of accumulation of succinate, a power signaling metabolite, will occur in result of disturbance or "break" locations in the TCA cycle. Elevated succinate suppresses prolyl hydroxylases and promotes HIF-1alpha protein stability, promoting transcription of glycolytic and proinflammatory genes (Huan *et al*., 2024). Succinate also stimulates mitochondrial reactive oxygen species (ROS) production with concomitant NF-kB activation (Vohwinkel *et al*., 2021). The formation of a succinate-HIF-1a axis has been reported in various infection and inflammation models and operates as a metabolic amplification loop between the inflammatory nuclear response and anaerobic glycolysis. Such amplification can be a tipping point in the lung where low amounts of succinate signaling can promote antimicrobial defense and adaptation in the lung; on the other hand, uncontrolled accumulation can tip the balance towards immunopathology (Lu, *et al*., 2025).

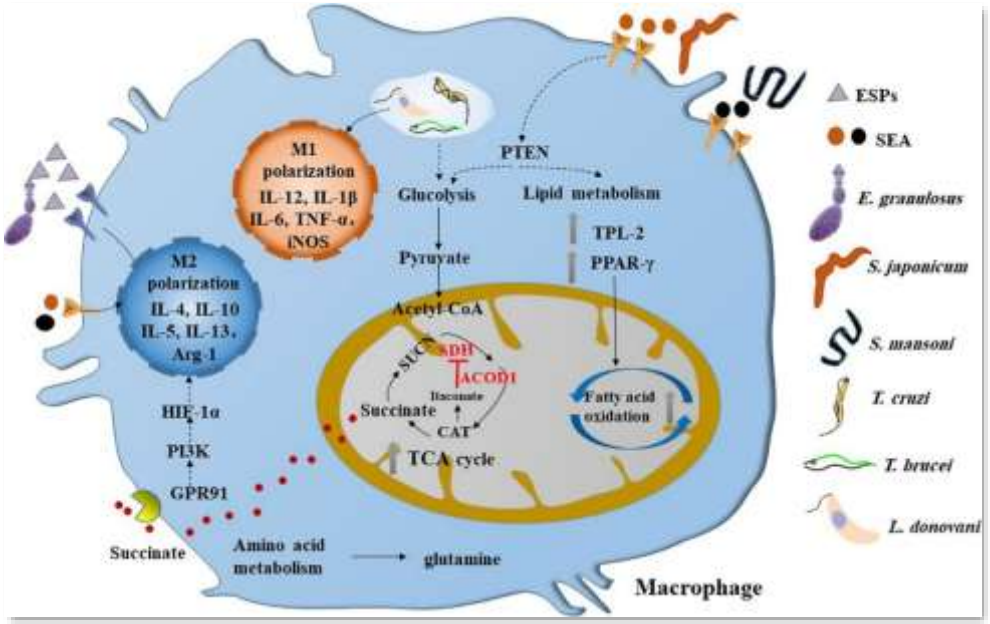

Figure 2: Macrophage reprogramming-immunometabolic during infection Succinate and itaconate are two key TCA-derived metabolites that are important for macrophage polarization. M1 macrophages metabolise using glycolysis and the pro-inflammatory cytokines (IL-1 beta, IL-6, TNF-A) whereas M2 use fatty acid oxidation and amino acid metabolism to encourage anti-inflammatory functions (IL-4, IL-10, Arg-1). Various pathogens (eg, *E granulosus*, *S japonicum*, *T cruzi*) manipulate these metabolic pathways so as to escape immune responses.

4.3 encias-Reducing NAD+, Sirtuins and Redox Regulation

The redox cofactor NAD+ (and its ratio with NADH) is an important fulcrum in cellular metabolism, connecting the glycolysis, TCA, and oxidative phosphorylation as well as the redox balance. Sirtuins (SIRT1 - 7) are the NAD^+ - dependent deacetylases which represent the metabolic sensors and regulators (Fiorentino *et al*., 2024). In states with high levels of glycolysis, intracellular NAD+ might become depleted, inhibiting sirtuin activity and compromising both mitochondrial and antioxidant programmes. Replenishing NAD+ (e.g., nicotinamide ribosome or NMN) is a pleasant approach to resaven the sirtuin signaling, enhance mitochondrial fitness, lessen ROS and reset inflammation (Yusri *et al*., 2025). Nature Reviews on Sirtuins and NAD role in Immune Cell Metabolism, Macrophages and T Cells Role of NAD in Macrophages, Sirtuins role in T Cells Because NAD+ is a substrate for several enzymes (PARPs, CD38, sirtuins) its regulation during infection stress becomes a competitive resource, particularly under immunological stress conditions on metabolic substrate (Mann, 2025).

4.4 Glycolysis or Fatty Acid Oxidation (FAO) Switch

One of the most basic metabolic choices that immune cells make is making a trade between glycolysis (rapid energy, biosynthesis, inflammation bias) or fatty acid oxidation/Fatty acid oxidation in mitochondria (FAO) (sustained energy, repair, tolerance). In acute activation (viral or bacterial challenge), immune cells preferentially use glycolysis for provision of substrates for biosynthesis and effector functions (cytokine secretion, proliferation etc.). Likewise, movements to a resolution, repair or memory state often involve a return to FAO and oxidative metabolism (Pearce & Pearce, 2018; O'Neill *et al*., 2016). The metabolic switch in the lung environment is limited by the availability of substrates: widgets can derive substrates for FAO from the lining lung lipids, and(a) glucose could be rate-limiting likewise in determinate in alveolar or interstitial areas. Thus, macrophage or T cell intrinsic

dynamic rewiring between glycolysis and FAO, metabolic flexibility, may decide whether inflammation is resolved or chronic (Wang *et al*., 2023; Lee *et al*., 2024). Therapeutic interventions that promote FAO (those that act as activators of peroxisomes (PPAR agonists), activators of adipose tissue AMP kinase (AMPK activators), uncouplers of mitochondria) are being explored as a way to induce a shift towards repair states to alleviate chronic inflammation in models of pulmonary disease (Liu *et al*., 2025; Zhao *et al*., 2024).

4.5 Amino Acid Metabolism

Amino acid metabolism is a very important regulatory module of immunometabolic networks under respiratory infections. In terms of the biological activity of arginine as a substrate of both nitric oxide synthase (NOS) and arginase, the effects of this amino acid appear to be paradoxical, as they are strongly immunological. NOS-derived Nitric Oxide (NO) is part of the antimicrobial defense but overproduced, on the one hand, can decrease the mitochondrial respiration, and, on the other hand, arginase-derived ornithine promotes tissue repair and polyamine synthesis, which leads to macrophage polarization toward anti-inflammatory phenotypes (Canè *et al*., 2025; Li *et al*., 2025). In addition, like alternative defensive effector cells that be stimulated through TLR 4-dependent signaling, the metabolization of tryptophan by means of indoleamine 2,3-dioxygenase (IDO) generates kynurenine and kynurenine metabolites along with immunoregulatory results, such as modulating activation of T-cells and triggering local immune tolerance (Seo *et al*., 2023). Glutamine metabolism is further categorized as incorporating energy yield with synthetic and antioxidative actions leading to anaplerotic flow into tricarboxylic acid (TCA) cycle videogravimetric pathway, nucleotide synthesis and glutathione-mediated redox homeostasis (Kielbowski *et al*., 2025). Importantly, in the context of respiratory infections both host immune cells and pathogens compete for these amino acid pools, and nutrient depleting activity of microbes may result in topping up host immunity, in favor of pathogen establishment (Starikova *et al*., 2023). Therefore, therapeutic manipulation of amino acid metabolic pathways by either arginine supplementation, IDO inhibitors or glutamine metabolism modulators, is a promising candidate for host-directed therapy in infectious lung diseases.

5. Human Metabolomic Evidence elaborates on disease endotypes

An increasing number of human cohort studies have characterized human respiratory infection metabolomes, including COVID-19, in the plasma, serum, BALF and urine. Some of the most prominent changes are increases in the concentration of lactate, in the ratios of amino acids (e.g. higher kynurenine, low tryptophan), deregulation of lipid profiles (e.g. ceramides, phospholipids), and disturbances in energy metabolites, such as the TCA cycle intermediates (Pimentel *et al*., 2024; Garcia-Lopez *et al*., 2025). These signatures are mostly associated with disease severity, ARDS development and mortality risk (Marin-Corral *et al*., 2021; Chatelaine *et al*., 2023). aHowever, we still face several issues: high interindividual variability (age, comorbidities, therapy), batch effects among metabolomics platforms, a lack of localized information of lung tissue level metabolomics. Some studies suggest separate metabolic endotypes of patients with elevated glycolytic/oxidative disruptions ("hyperinflammatory") and reduced shifts ("metabolic suppressed"). Fundamental Gondesa: Metabolomics, coupled to transcriptomics, proteomics, and deep immune phenotyping, can be used to segregate patients into mechanistically novel metabolic phenotypes, serving as rational stratums into which patients could be allocated for specific therapeutic agents.

6. Host Directed Metabolic Interventions

Given the causal-ness of metabolic reprogramming, this suggests that metabolic nodes are targets of translational promise. Among the leading strategies are glycolysis inhibitors or HIF inhibitors (2-deoxyglucose, small molecule HIF antagonists) to reduce pathological inflammation while not diminishing antiviral function, 2-deoxyglucose (2-DG) demonstrated antiviral and anti-inflammatory efficacy both in cell and animal models as well as in a phase II study as adjunct treatment for patients with Covid-19, where 2-DG also seemed to accelerate clinical recovery (Bhatt *et al*., 2022; Chen *et al*., 2023; Huang *et al*., 2022). Blocking glycolysis using 2-DG inhibits the expansion of the infection of the SARS-CoV-2 Floyd virus and decreases progeny infectivity in cell culture (Chen *et al*., 2023). Itaconate Derivatives (e.g., 4-octyl itaconate, dimethyl itaconate) Itaconate derivatives are attractive modulators of inflammation and viral replication, but the effects of these compounds may be different in different cell types in the lungs. In the influenza models itaconate and its derivatives suppressed inflammation and virus load (Sohail et al., 2022). In models of infection with the novel coronavirus (SARS-CoV-2), prophylactic and therapeutic treatment with itaconate reduced lung injury (jiang *et al*., 2025). However, it is in the context specific risks that are to be considered including alveolar macrophages where native itaconate was found as exacerbating the production of the inflammdzory molecule NLRP3 and leading to lung pathology-in this case injury (Shan *et al*., 2025). NAD^+ boosters/ sirtouin activators (eg. nicotinamide riboside, NMN) are attractive, considering their potential to improve the mitochondrial resilience and redox balance. Although direct trials regarding respiratory viral infection are limited, NAD^+ augmentation is being explored across a large body of work in immunometabolic and aging. Other metabolic modulators, such as metformin, fumarate derivatives, statins might either modulate the mitochondrial energetics or activate the AMPk or influence the Nrf2 pathways. Some observational clinical

data has suggested that metformin use is linked to improved outcomes from people with Covid, perhaps through metabolic modulation (Chen *et al*, 2023). Combinatorial types of regimens matching metabolic modulators with antivirals, antibiotics or immunomodulators may offer benefit and reduce off-target risks of use. In influenza and *S. aureus* treatment preclinical models, the lung injury and lung inflammation were reduced by metabolic interventions (Jiang *et al*., 2025; He *et al*., 2024). However, translation to trials of human respiratory infection is still in its infancy. Important aspects to consider are safety, optimal timing (early vs. late), dosing regimens and potential for immunosuppression or metabolic toxicity. A pragmatic transcultural approach to translation would involve stratifying patients on their metabolic endotype; then only those patients will benefit from the application of metabolic intervention strategies with evidence of maladaptive glycolytic reprogramming/metabolic dysregulation; metabolic biomarker(s) and other immunologic biomarker(s) will be evaluated longitudinally in equivalence trials. A pragmatic transcultural approach to translation would involve stratifying patients on their metabolic endotype; then only those patients will benefit from the application of metabolic intervention strategies with evidence of maladaptive glycolytic reprogramming/metabolic dysregulation; metabolic biomarker(s) and other immunologic biomarker(s) will be evaluated longitudinally in equivalence trials.

Discussion

they have colligated emerging evidence that immunometabolic reprogramming is a mediator in respiratory infection pathogenesis modulating the balance that governs host defense, immunopathology, and resolution. The metabolic reprogramming caused by pathogens such as increased glycolytic pathways, TCA cycle metabolite shuttling and lipid and amino acid reprogramming is not a passive byproduct of infection, but an active component determining immune cell behaviour. These metabolomic alterations modulate cytokine responses, tissue injury and repair pathways through changes in substrate flow, redox balance and signaling; the knowledge of these metabolic changes can provide a roadmap for host directed therapies. Proof of concept *in vitro* and animal model systems have been established. Viruses from the respiratory lineage such as influenza and SARS-CoV-2 activate glycolysis and inhibit mitochondrial flux as mechanisms for viral replication and pro-inflammatory amplification. In addition, macrophage succinate accumulation can strengthen the signaling of HIF-1a and itaconate metabolic pathways play a role as feedback modulator of inflammatory pathways. Insights into disease severity, ARDS and clinical outcomes in human cohorts also show that relatively high plasma lactate and succinate, disturbed kynurenine/tryptophan pairs and lipid species (e.g. ceramides) serve as positive correlates for disease severity, ARDS and mortality risk (Cevenini *et al*., 2024; Metabolomic Insights into COVID-19 Severity, 2024). Mechanistic hypotheses about human biology are then based on these clinical data, and suggest that metabolic phenotypes may be used to inform patient stratification. However, there are a number of barriers in interpretation. Many mechanistic aspects are based on acute infection animal models or cell lines at high doses, but in humans, we experience a heterogeneous disease, that becomes chronic and is modified by comorbidities, treatments and time-dependent processes. Longitudinal metabolomics (following patients from preinfection to recovery) are very few. Techniques to fill this gap will include isotope flux tracing in ex vivo human lung or immune systems cells, spatial metabolomics in lung biopsies or autopsy, and patterns integration across transcriptomic, proteomic and/or cellular datasets. An issue may be contextuality and heterogeneity. The same metabolic pathway may all perform differently, in ways that are beneficial or detrimental, depending on the type of cell, the microenvironment, the stage of disease, and the burden of pathogen. The case of itaconate illustrates such complexity: while in many situations itaconate has been suggested to be anti-inflammatory, in alveolar macrophages the excess of itaconate was found to increase the impact of the NIR primed inflammasome and poor lung injury (Shan *et al*., 2025). Findings from macrophage cells that are derived from monocytes or that circulate in the blood may fail to directly translate to resident populations in the lung. Similarly, interventions that blunt glycolysis could be effective at suppressing inflammation but could have a detrimental effect on controlling pathogens and repairing tissues. Metabolic programming also interfaces with the host factors such as age, metabolic diseases (e.g. diabetes), nutritional status, oxygenation gradient and co-infections. For example, hyperglycemia has been known to increase the glycolytic responses caused by the presence of the viral agent indicating that glycolytic responses induced by the protease inhibitor get worse in the presence of hyperglycemia. Differences among virus variants (Delta vs Omicron) in inflammatory and metabolic stress provide further dissertation that metabolic targeting is patho-pathogen patient-specific. Attacks on immunometabolic checkpoints are exciting-but also come with real danger. Candidate interventions are glycolytic inhibitors, HIF antagonists, itaconate derivatives, NAD++ boosters, repurposed metabolic regulators (metformin, fumarates). However, safety, dosing windows and unintended immunosuppression are a major concern. Over-suppression of glycolysis could negatively impact clearance of pathogens, metabolic agents could interact with concomitant medications, and systemic metabolic changes could be at risk for off-target effects. The paradoxical inflammatory effect of endogenous itaconate in alveolar macrophages as a caution from a one size fits all application. Even forms of derivatives (such as 4-octyl itaconate) require strict validation in lung tissue-residents. Notably, 4-octyl itaconate was recently found to rescue mitochondrial dysfunction and suppress the action of the inflammasome activator protein 3 (NLRP3) in pyroptosis in models of macrophages, leading to the improvement of acute respiratory distress syndrome (ARDS) - like

injury (Wu *et al*., 2023). A promising way forward is precision metabolic therapy based on patient metabolic endotypes. Patients with hyper glycolytic/metabolic suppression can potentially be treated with glycolysis modulators and NAD or mitochondrial support respectively. Through the integration of metabolomic and immunophenotyping readouts into clinical trial design, we will achieve dynamic intervention optimization based upon feedback.

Limitations and Caveats

Many mechanistic studies are based on modeling cell types (bone marrow derived macrophages) which are greatly simplified, and do not mimic the lung niche. For human tissues causality versus correlation is hard to interpret because we lack flux tracing (isotope labeling). Human metabolomic signatures are susceptible to confounding background factors (medications, diet, diminished or increased exposure to smoking) as well as batch effects in catch analyses and discrepancies in sample processing procedures. Temporal resolution is often very low: few studies follow the transition of metabolism during the whole infection, recovery, and the long COVID phases. Stem cell interaction with other cell types (endothelium, fibroblast, epithelial barrier) and transcript passage between cell space is underexplored.

Future Directions

1. Comprehensive single-cell to tissue metabolic phenotyping of human lung samples (BAL), using single-cell and spatial metabolomics in longitudinal and spatial directions (autopsy, bronchoscopic biopsies).
2. Isotope flux tracing in ex vivo clinical human lung/immune cells to establish migration of intracellular metabolic pathways and directionality;
3. Metabolically defined endotype stratification of patient cohorts to inform allocation of host directed therapy.
4. Combination therapy: part treatment with metabolic modifiers and the use of antivirals, immuno-modulators or lung-protective efforts.
5. Together, conditional and conserved cell-type-specific mouse models: ACOD1, SDH, sirtuins transgenic/knockout mice in AMs, epithelial cells.
6. Metabolic modulators for tolerability dose finding studies in chronic infections of the respiratory tract in humans.

Conclusion

This review points out immunometabolic reprogramming as a central determinant of the outcome of respiratory infections, controlling the balance between antiviral/antibacterial immunity, tissue damage and resolution. Across a range of pathogens (influenza, RSV, and most critically, recently, the novel coronavirus (Sars-Cov-2) as well asummies. tuberculosis), infection drives extensive metabolic remodeling especially in glycolysis, in tricarboxylic acid cycle intermediates, in lipid synthesis and in amino acid metabolism. These changes are not simply passive by-products of infection, but active determinants of immune cell phenotype, cytokine production and pathogenesis. Metabolic cages including the itaconate/IRG1, succinate/HIF-1a and NAD+/sirtuin axes emerge as nodes providing connections between cellular bioenergetics and inflammatory signaling. The importance of these pathways is further supported by human metabolomic studies demonstrating the presence of metabolic signatures that are associated with the severity of disease, ARDS and long-term complications, such as post infective syndromes. Therapeutically, host-directed metabolic interventions, such as glycolysis inhibitors, itaconate derivatives, mitochondrial boosters and NAD+ precursors, hold great promise for rebalancing immune responses and restricting immunopathology. However, context dependence, inter-patient variability and the dual roles of a large number of metabolic pathways require precision approaches based on metabolic endotyping, longitudinal phenotyping and mechanistic validation in human tissues. The future will see studies combining spatial multi-omics, isotope flux tracing and clinical metabolic profiling, which will be the important to defining the best targets, timing and dosing of metabolic therapies. By exploiting mechanistic insights together with translation innovation, it appears the field is well positioned to harness the power of immunometabolism for next-generation immunotherapies against acute and chronic respiratory infections.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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