Review

Immunometabolic Reprogramming in Disease: From Energy Homeostasis and Inflammatory Signaling to Therapeutic Targeting Across Organ Systems

Seyyedeh Elaheh Mousavi[1], Shima Davoudi[2], Elham Soleimani[3*]

[1] Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

[2] Neurophysiology Research Center, Institute of Neuroscience and Cognition, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[3] Department of Neuroscience, School of Advanced Technologies in Medicine, Hamadan University of Medical Sciences, Hamadan, Iran.

***Corresponding author:** Elham Soleimani, School of Advanced Technologies in Medicine, Hamadan University of Medical Sciences, Hamadan, Iran. E-mail: el.soleymani65@gmail.com

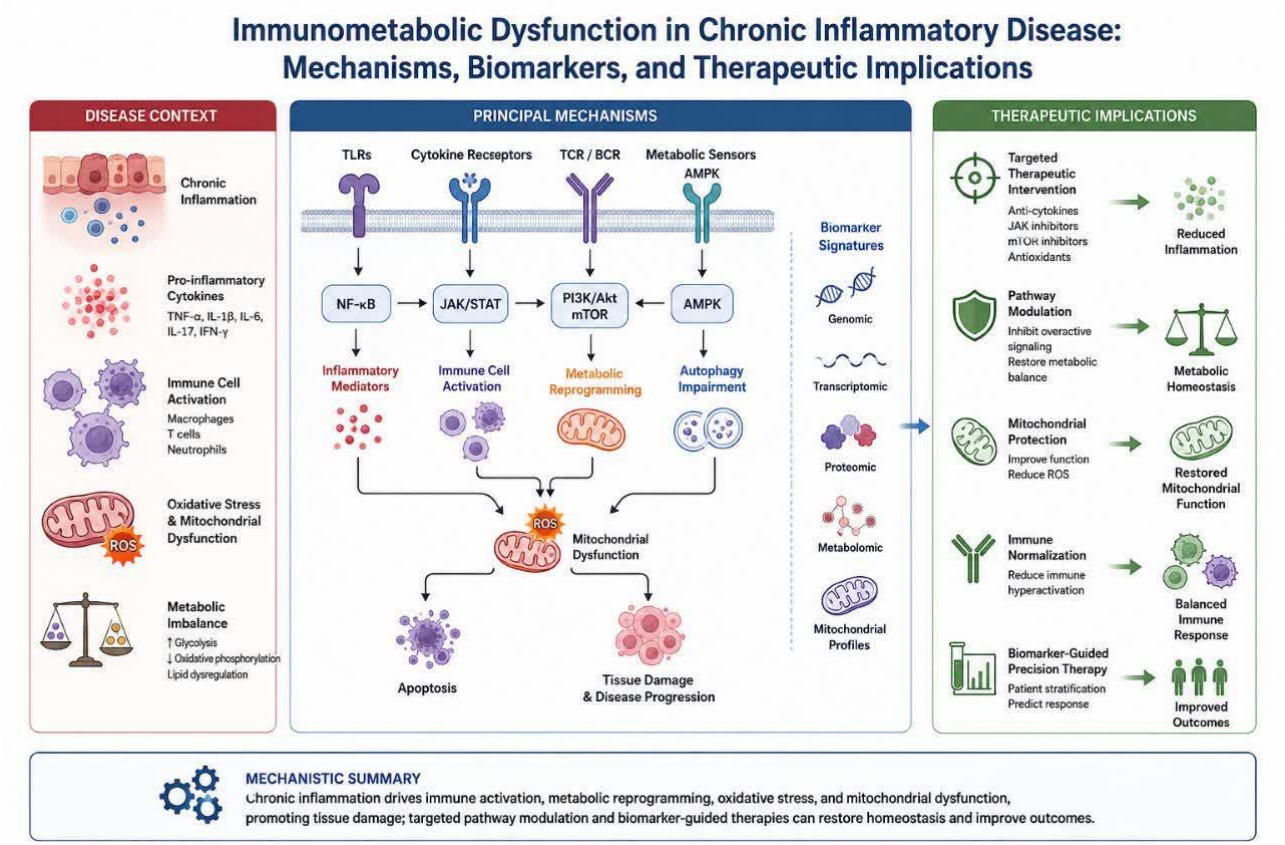
Receive Date: 15 June 2026; **Revise Date:** 30 July 2026; **Accept Date**: 03 August 2026; **Publish Date:** 06 August2026.

Nexus of Pathophysiology and Therapeutics (NPT). 2026;1(1): 013, https://doi.org/10.22034/npt.2026.1.013

Abstract:

Immune and metabolic processes are increasingly recognized as interconnected determinants of disease progression. Immunometabolic reprogramming describes the dynamic adaptation of cellular energy metabolism and immune function to environmental and pathological stress, with persistent dysregulation contributing to chronic inflammation, metabolic dysfunction, and tissue injury. This review develops a systems-level framework for understanding how energy sensing, inflammatory signaling, mitochondrial function, and organ-specific metabolic states interact to shape disease phenotypes. We examine the central role of the AMPK–mTOR axis, metabolic switching between oxidative phosphorylation and glycolysis, and inflammatory pathways involving NF-κB and cytokine networks in coordinating immune–metabolic responses. Particular emphasis is placed on mitochondria as an integration hub linking bioenergetic status, redox signaling, and inflammatory activation. Organ-specific manifestations across the liver, adipose tissue, brain, and cardiovascular system are discussed to illustrate how shared immunometabolic principles generate distinct tissue phenotypes. We further consider evidence from systems biology and multi-omics approaches, highlighting their potential to identify network-level disease signatures, mechanistic subtypes, and therapeutic vulnerabilities. Current therapeutic strategies targeting AMPK, mTOR, inflammatory signaling, oxidative stress, and mitochondrial dysfunction are evaluated, with emphasis on the limitations of single-pathway interventions and the emerging rationale for integrated or combination approaches. Finally, the translational potential of composite immune–metabolic biomarkers, precision immunometabolic stratification, computational modeling, and adaptive therapeutic monitoring is discussed. Collectively, immunometabolic reprogramming provides a unifying framework that connects systemic energy homeostasis with inflammatory signaling and organ dysfunction, offering a mechanistic basis for the development of more precise and durable therapeutic strategies across diverse disease states.

Keywords: Immunometabolic reprogramming; Immunometabolism; Energy homeostasis; Inflammation; Mitochondrial dysfunction; Systems biology



Graphical Abstract: Immunometabolic Reprogramming: A Systems Framework Linking Energy Homeostasis, Inflammation, and Organ Dysfunction. Immunometabolic reprogramming involves a bidirectional interaction between metabolic dysfunction and immune activation. Disrupted AMPK–mTOR signaling, mitochondrial dysfunction, and excessive ROS generation promote inflammatory pathways such as NF-κB and inflammasome activation, while TNF-α, IL-6, and IL-1β further impair insulin signaling and cellular metabolism. This self-reinforcing metabolic–inflammatory loop drives persistent dysfunction across the liver, adipose tissue, brain, and cardiovascular system, contributing to diverse chronic diseases. Overall, the figure highlights immunometabolic dysfunction as a network-level process and supports integrated therapeutic strategies targeting metabolism, inflammation, and mitochondrial homeostasis.

Introduction

Immune and metabolic systems are tightly interconnected in human biology. This relationship is increasingly recognized as a fundamental determinant of disease susceptibility, progression, and therapeutic response. Many acute and chronic disorders involve simultaneous immune activation and metabolic dysfunction (1-3). Historically, these fields were studied separately. Immunology focused on host defense and inflammation, while metabolism was viewed mainly as energy production. This separation shaped most experimental and clinical frameworks. This view is no longer sufficient. Immune cells depend strongly on metabolic state, and metabolic tissues actively respond to inflammatory signals (1, 3, 4). This establishes a continuous bidirectional interaction between immune and metabolic processes. Earlier studies often treated metabolism as a passive background for immune activity. This assumption is now outdated. Immune activation requires rapid metabolic reprogramming, while immune mediators directly reshape metabolic pathways (1, 3, 5). These interactions are dynamic and context-dependent. A major limitation of previous research is its pathway-centric approach. Most studies focus on single signaling cascades or isolated molecular targets, including cytokines, kinases, or transcription

factors. While informative, this reductionist view fails to explain system-level disease behavior. Many diseases involve network-level dysfunction across multiple tissues and organs (6-8). Single-pathway targeting often produces only partial or transient therapeutic effects due to compensatory mechanisms. A systems physiology approach provides a more complete framework. It integrates immune, metabolic, and organ-level functions into a unified model. Disease is therefore viewed not as a linear cascade but as a state of network imbalance, where disturbances in one node propagate across biological systems. This concept is increasingly supported by multi-omics studies, which demonstrate coordinated metabolic and inflammatory alterations across diverse disease states (7, 9). The aim of this review is to develop a unified framework for immunometabolic reprogramming in disease. We focus on how systemic energy homeostasis interacts with inflammatory signaling across organ systems and how these interactions shape disease progression and therapeutic response. Immunometabolic reprogramming describes the adaptive and maladaptive changes in immune and metabolic systems under stress conditions, ultimately influencing cellular, tissue, and whole-organism physiology (3, 5). In health, this system is flexible and adaptive. In disease, it becomes dysregulated and persistent. Metabolic stress reinforces inflammation, and inflammation further disrupts metabolic balance. This self-sustaining loop contributes to chronic disease progression (1, 10). Understanding this framework is essential for modern biomedical research. It supports more precise therapeutic strategies and encourages interventions that target multiple levels of biological organization (3). Overall, immunometabolic reprogramming represents a shift in how disease is understood. It integrates immune signaling, metabolic regulation, and organ-level physiology into a unified conceptual framework. This perspective provides a more realistic view of disease biology and opens new directions for therapeutic innovation.

Systems Architecture of Energy Homeostasis and Immune Regulation

Energy homeostasis is a core determinant of immune behavior. Cells constantly sense nutrient status and adjust their functional state accordingly. This regulation is not auxiliary. It sits at the center of immune activation and resolution (3, 5, 11, 12). At the cellular level, energy sensing is mainly coordinated by the AMPK–mTOR axis. AMPK is activated under low energy conditions. It promotes catabolic pathways and restores ATP balance. mTOR responds to nutrient abundance and drives anabolic activity. It also supports immune cell growth and effector functions. The balance between these two pathways shapes immune responsiveness in real time (5, 11, 13). Nutrient availability directly influences immune cell fate. Under nutrient-limited conditions, immune cells may adopt more energy-conserving or regulatory phenotypes, depending on cell type and cellular context. When nutrients are abundant, they shift toward activation and proliferation. This metabolic reprogramming is not merely secondary to immune activation; rather, it is integral to immune cell function and effector activity (12, 14).

Immune activation is also associated with metabolic switching. Resting immune cells rely mainly on oxidative phosphorylation for energy efficiency. Activated immune cells shift toward glycolysis, even in oxygen-rich environments. This metabolic reprogramming supports rapid ATP generation and biosynthetic demand. It also facilitates production of inflammatory mediators (3, 12, 15). These metabolic states are not independent. They are dynamically regulated based on environmental and intracellular signals. The transition between oxidative metabolism and glycolysis is reversible but tightly controlled. It reflects the functional needs of the immune system at each stage of response (3, 12, 16). A key feature of this system is the presence of feedback loops between energy balance and immune tone. Metabolic stress enhances inflammatory signaling. In turn, inflammatory mediators further disrupt metabolic pathways. This creates a self-reinforcing circuit that can stabilize

either homeostasis or pathology depending on context (12, 17). In chronic disease, this regulatory system becomes dysregulated. Persistent nutrient excess, hypoxia, and mitochondrial dysfunction can shift the balance toward sustained immune activation. In several chronic disease contexts, AMPK activity is reduced, whereas mTOR signaling and glycolytic programs may remain relatively elevated. This contributes to chronic low-grade inflammation and progressive tissue dysfunction. Overall, immune function is tightly governed by metabolic architecture. Energy sensing pathways, nutrient status, and metabolic switching collectively define immune cell behavior. Disruption of this architecture leads to persistent immune activation and loss of physiological balance (11, 12, 16).

Inflammatory Signaling as a Driver of Metabolic Reprogramming

Inflammatory signaling is not only a defensive response. It is a direct regulator of metabolic state. Once activated, immune pathways rapidly reshape cellular energy programs. This creates a strong bidirectional link between inflammation and metabolism (12, 18). Cytokine networks are central to this process. Key mediators such as TNF-α, IL-6, and IL-1β act across multiple tissues and can influence systemic metabolic homeostasis. They influence insulin sensitivity, mitochondrial function, and substrate utilization. Their effects are not localized. They propagate systemically and affect metabolic balance across organs. TNF-α is strongly associated with insulin resistance. It interferes with insulin receptor signaling and reduces glucose uptake in peripheral tissues. IL-6 shows context-dependent effects but is consistently involved in chronic inflammatory states. IL-1β contributes to metabolic stress by altering pancreatic and hepatic function (18, 19).

These cytokines converge on intracellular signaling hubs. NF-κB is one of the central regulators. Once activated, it drives transcription of inflammatory genes while also modifying metabolic enzyme expression. This dual role positions NF-κB as a key link between immune activation and metabolic reprogramming. Inflammation also disrupts insulin signaling pathways. Chronic inflammation alters IRS-1 phosphorylation, thereby impairing downstream PI3K–AKT signaling and glucose transport (12, 18, 20-22). A key concept in this context is the chronic inflammatory set-point. In many diseases, inflammation does not fully resolve. Instead, it stabilizes at a persistent low-grade level. This state is not static. It is actively maintained by feedback between immune and metabolic systems. Metabolic stress reinforces inflammatory signaling. At the same time, inflammation further destabilizes metabolic control. This creates a self-sustaining loop that is difficult to interrupt once established (18, 23, 24). In chronic disease, this loop becomes dominant. Mitochondrial dysfunction, nutrient excess, and tissue stress all contribute to its persistence. The system shifts away from homeostasis and toward a stable pathological state. Overall, inflammatory signaling functions as a metabolic reprogramming system. It reshapes energy utilization, disrupts insulin signaling, and establishes feedback loops that can stabilize chronic disease states (12, 17, 25).

Organ-Specific Immunometabolic Reprogramming

Immunometabolic reprogramming does not occur uniformly across the body. Each organ shows a distinct response profile based on its metabolic demand, immune environment, and functional role. However, the underlying pattern is consistent. Immune activation and metabolic dysfunction evolve together in a tissue-specific manner (12, 26).

- Liver

The liver is a central hub for metabolic and immune integration. It regulates glucose and lipid homeostasis while also participating in systemic inflammatory responses (27). During inflammation, hepatocytes shift toward an acute-phase response. This includes increased production of proteins such as CRP and fibrinogen. While protective in the short term, this response alters systemic metabolic

balance (28). Chronic inflammation disrupts hepatic lipid and glucose metabolism. Insulin signaling becomes impaired. Lipid accumulation increases. Over time, this contributes to metabolic disorders such as fatty liver disease and insulin resistance (28-31). The liver therefore acts as both a metabolic regulator and an immune-responsive organ. Its dual role makes it highly sensitive to immunometabolic stress (32).

- Adipose Tissue

Adipose tissue is no longer considered a passive energy storage site. It is an active immunometabolic organ (33). In obesity and metabolic stress, adipose tissue undergoes immune cell infiltration. Macrophages become a prominent immune cell population within inflamed adipose tissue. These cells shift toward a pro-inflammatory phenotype (33-35). Adipokine signaling is also disrupted. Adiponectin levels decrease, while leptin and pro-inflammatory mediators increase. This imbalance contributes to systemic inflammation and insulin resistance. Adipose tissue therefore acts as a major amplifier of systemic immunometabolic dysfunction (18).

- Brain

The brain has high and continuous energy demands. It is highly sensitive to metabolic disturbances and inflammatory signaling (36). Neuroinflammation is a key feature of many neurological disorders. Microglial activation plays a central role in this process. Once activated, microglia produce inflammatory mediators that alter neuronal function (37, 38). Energy failure further exacerbates this state. Mitochondrial dysfunction and impaired glucose utilization lead to synaptic instability (39). This affects neural network function and cognitive processes. The brain is therefore particularly vulnerable to combined metabolic and inflammatory stress (40).

- Cardiovascular System

The cardiovascular system is strongly influenced by immunometabolic interactions. Endothelial cells are central regulators of vascular homeostasis (41). Under inflammatory conditions, endothelial function becomes impaired. Nitric oxide signaling is reduced. Vascular tone regulation is disrupted. This leads to endothelial dysfunction, a key early event in vascular disease (42). Chronic inflammation promotes vascular remodeling. Smooth muscle cell proliferation increases (43). Lipid deposition and immune cell infiltration contribute to atherosclerotic plaque formation. These processes collectively link metabolic dysfunction with cardiovascular disease progression. Overall, organ-specific immunometabolic reprogramming reflects a coordinated but tissue-dependent response to systemic stress. While each organ exhibits unique features, all share a common pattern of coupled metabolic and inflammatory disruption (44) (Table 1).

Mitochondria as the Central Integration Hub

Mitochondria occupy a central position in immunometabolic regulation. They are not only energy-producing organelles. They also function as signaling platforms that connect metabolism with immune activity (45). In many diseases, mitochondrial function becomes impaired. This bioenergetic failure reduces ATP production and limits cellular flexibility. Tissues with high energy demand are particularly affected. Over time, this contributes to progressive organ dysfunction (46). Mitochondrial dysfunction is also closely linked to redox imbalance. Reactive oxygen species (ROS) are generated as by-products of oxidative phosphorylation. Under physiological conditions, ROS act as signaling molecules. They help regulate adaptation and stress responses (47).

When mitochondrial function is disrupted, ROS production increases beyond physiological levels. This shift changes ROS from signaling mediators into drivers of cellular damage and inflammation. A key feature of this system is the feedback loop between mitochondria and immune signaling (48). Mitochondrial stress activates inflammatory pathways such as NF-κB and inflammasome

signaling (49). In turn, inflammatory mediators further impair mitochondrial function. This creates a self-reinforcing cycle (50). As this cycle progresses, metabolic stability declines. Cells shift away from efficient oxidative metabolism toward glycolytic pathways. This metabolic shift supports short-term survival but reduces long-term efficiency. In parallel, inflammatory signaling becomes more persistent (51).

Organ	Key metabolic role	Immune response pattern	Disease outcome
Liver	Glucose and lipid homeostasis	Acute-phase inflammatory response	Fatty liver disease, insulin resistance
Adipose tissue	Energy storage and endocrine signaling	Macrophage-driven inflammation	Obesity-related metabolic syndrome
Brain	High energy demand, neuronal signaling	Microglial activation and neuroinflammation	Neurodegeneration, cognitive decline
Cardiovascular system	Vascular regulation and perfusion	Endothelial inflammation and remodeling	Atherosclerosis, heart failure

Table 1. Organ-specific features of immunometabolic reprogramming.

In advanced disease states, this process contributes to metabolic collapse. Energy production becomes insufficient to meet tissue demands. At the same time, inflammatory activity remains elevated. This imbalance accelerates tissue damage and functional decline (52). Because of this central role, mitochondria are increasingly considered therapeutic target nodes. Interventions that restore mitochondrial function or reduce oxidative stress may help break the cycle of immunometabolic dysfunction. These strategies aim to restore both energy balance and immune regulation rather than targeting a single pathway (53). Overall, mitochondria function as a central integration hub linking energy metabolism with immune signaling. Their dysfunction represents a key driver of both metabolic imbalance and chronic inflammation across multiple disease states (Table 2).

Mitochondrial feature	Pathological change	Downstream effect	Clinical relevance
ATP production	Reduced oxidative phosphorylation	Energy deficit	Organ dysfunction, fatigue syndromes
ROS signaling	Excessive ROS generation	Oxidative stress and inflammation	Chronic inflammatory diseases
Metabolic flexibility	Shift toward glycolysis	Reduced efficiency	Cancer, immune activation states
Immune interaction	Activation of inflammasome pathways	Sustained inflammation	Multisystem chronic disease

Table 2. Mitochondrial alterations and their immunometabolic consequences.

Systems Biology and Multi-Omics Perspectives

Immunometabolic reprogramming cannot be fully understood through single-pathway analysis. The system operates across multiple biological layers. These include genes, transcripts, proteins, metabolites, and cellular networks. Systems biology provides the framework to integrate these layers into a coherent view (9, 54). Transcriptomic profiling has revealed distinct signatures associated with immunometabolic states (55). In inflammatory

conditions, genes related to glycolysis, cytokine signaling, and stress responses are consistently upregulated (56). At the same time, oxidative phosphorylation and mitochondrial gene programs are often suppressed (57). These coordinated changes suggest broader cellular reprogramming rather than isolated activation of individual pathways (55). Metabolomics has further strengthened this view (58). Changes in glucose utilization, lipid metabolism, and amino acid pathways are closely linked to immune activation states (12). Specific metabolic profiles can distinguish between acute inflammation, chronic low-grade inflammation, and resolution phases. This supports the idea that metabolism itself encodes immune status (59).

Network biology approaches provide an additional layer of insight. Instead of focusing on individual molecules, these methods map interactions between genes, proteins, and metabolites (58). In immunometabolic disease, network connectivity often becomes rewired. Key hubs such as NF-κB, HIF-1α, and mTOR emerge as central regulatory nodes. Disruption of these hubs can propagate system-wide effects (12). Integration of multilayer datasets is essential for a complete understanding of disease mechanisms. Combining transcriptomic, proteomic, and metabolomic data allows for more accurate disease phenotyping. It also improves identification of mechanistic subtypes within clinically similar conditions. This is particularly relevant in heterogeneous diseases such as sepsis, diabetes, and cancer (58). Computational modeling plays an increasingly important role in mechanistic discovery. Dynamic models can simulate interactions between immune and metabolic pathways under different conditions. These models help identify feedback loops, tipping points, and system stability thresholds. In some cases, they can also predict therapeutic response patterns based on network structure (54).

Therapeutic Targeting of Immunometabolic Pathways **Therapeutic strategies targeting** immunometabolic dysfunction are shifting from single-pathway inhibition toward integrated system modulation. This change reflects a broader understanding of disease as a network-level imbalance rather than a linear signaling defect (60, 61). AMPK activators are among the most studied metabolic modulators. By enhancing cellular energy sensing, AMPK promotes catabolic metabolism and improves metabolic flexibility. It also suppresses excessive inflammatory signaling (61, 62). Agents such as metformin indirectly engage this pathway and demonstrate both metabolic and anti-inflammatory effects in clinical settings (60, 61). mTOR signaling represents a complementary nutrient-sensing axis that, in contrast to AMPK, generally promotes anabolic activity, cellular growth, and immune activation. mTOR controls cellular growth, protein synthesis, and immune activation. Its inhibition reduces immune cell proliferation and dampens inflammatory responses. However, systemic suppression of mTOR can also affect tissue repair and normal immune function, which limits long-term use in some contexts (63). Anti-inflammatory metabolic therapies aim to directly link immune modulation with metabolic correction. These approaches target shared nodes between inflammation and metabolism rather than isolated cytokines. This includes interventions that reduce oxidative stress, restore mitochondrial function, or normalize glucose utilization in activated immune cells (60, 64).

Combination therapy is increasingly considered more effective than monotherapy. Disease processes are maintained by multiple redundant pathways. Targeting only one node often leads to compensatory activation of alternative routes (65, 66). Combining metabolic and immune modulators may produce more stable and sustained therapeutic outcomes (60, 61). Single-target interventions have clear limitations. They often produce partial responses or temporary improvement. In chronic diseases, feedback loops rapidly restore the pathological state. This reduces long-term efficacy and increases relapse risk (67). These limitations highlight the need for system-level intervention strategies (68, 69). Precision immunometabolic therapy represents a more advanced concept. It involves stratifying patients based on metabolic and

immune profiles. Treatment is then tailored to specific network dysfunctions rather than broad disease categories. This approach integrates biomarkers, functional data, and systems-level modeling to guide therapeutic decisions (70). Overall, effective therapeutic targeting of immunometabolic pathways requires a shift from isolated molecular interventions to integrated system-level strategies that address both metabolic dysfunction and immune dysregulation simultaneously.

Translational Biomarkers and Clinical Relevance

Translational biomarkers play a central role in linking immunometabolic mechanisms with clinical practice. They provide measurable signals of underlying immune and metabolic activity (9, 71). In immunometabolic diseases, single biomarkers are often insufficient. The dynamic and multilayered nature of immunometabolic regulation limits the ability of individual biomarkers to capture the complexity of disease states (72). Circulating cytokines are widely used markers of immune activation. TNF-α, IL-6, and IL-1β reflect inflammatory burden. However, their interpretation depends heavily on metabolic context. Similar cytokine levels may represent different disease states depending on energy balance and organ function. Metabolic markers add another layer of information. Glucose levels, lipid profiles, lactate, and insulin resistance indices provide insight into systemic metabolic status. When combined with inflammatory markers, they offer a more complete view of disease activity (73, 74). Biomarkers of mitochondrial function are receiving increasing attention. These include indicators of oxidative phosphorylation efficiency, ROS balance, and mitochondrial DNA release. Such markers reflect the integration point between energy failure and inflammatory activation (75). Composite biomarker panels are emerging as a more reliable approach. Instead of relying on a single variable, these panels integrate immune, metabolic, and mitochondrial signals. This improves both sensitivity and specificity in disease characterization (9). It also better reflects the network nature of immunometabolic dysfunction (69). Disease stratification is one of the most important applications of these biomarkers. Patients with similar clinical diagnoses may have very different underlying immunometabolic profiles. Biomarker-based phenotyping helps identify these subgroups. This can improve prognosis and guide therapeutic decisions (76-78).

It is also important to distinguish between diagnostic and predictive utility. Diagnostic biomarkers identify the presence of disease. Predictive biomarkers estimate disease progression or treatment response (79, 80). In immunometabolic disorders, predictive markers are often more clinically valuable, as they reflect dynamic system behavior rather than static disease states. Overall, translational biomarkers provide a critical bridge between mechanistic immunometabolic research and clinical application. Their greatest value lies not in isolation, but in integrated interpretation across immune, metabolic, and mitochondrial domains (9, 10, 71, 72).

Disease Applications Across Organ Systems

Immunometabolic reprogramming is a shared underlying mechanism across a wide range of human diseases. Although clinical presentations differ substantially between organ systems, the core biological pattern remains consistent (5, 12). Immune activation and metabolic dysfunction evolve together and reinforce each other over time. This interaction is dynamic, context-dependent, and often self-sustaining (81).

- Metabolic diseases

Obesity and type 2 diabetes represent prototypical examples of immunometabolic dysfunction (82). Chronic excess nutrient availability leads to sustained metabolic stress. This state triggers low-grade, persistent inflammation rather than acute immune activation (83). Adipose tissue plays a central role in this process. As adipocytes expand, local hypoxia and cellular stress signals increase. This promotes infiltration of immune cells, particularly pro-inflammatory macrophages. These

immune cells shift adipose tissue from an energy storage organ into an active inflammatory site. At the same time, adipokine secretion becomes dysregulated. Protective signals such as adiponectin decrease, while pro-inflammatory mediators increase. This imbalance directly worsens systemic insulin sensitivity (84). The liver is also affected early in disease progression. Hepatic lipid accumulation and impaired insulin signaling contribute to systemic metabolic inflexibility (85). Over time, metabolic and inflammatory loops become self-reinforcing, driving progressive disease severity (86-88).

- Cardiovascular diseases

Cardiovascular pathology is strongly shaped by immunometabolic interactions (89, 90). Endothelial cells are highly responsive to inflammatory and metabolic stress signals. When exposed to chronic inflammation, endothelial function becomes progressively impaired. A key early event is the reduction of nitric oxide bioavailability. This disrupts vascular relaxation and promotes endothelial dysfunction (91, 92). In parallel, lipid retention and immune cell adhesion increase within the vascular wall. Importantly, atherosclerosis is not only a lipid storage disorder. It is a chronic inflammatory process layered on top of metabolic dysfunction. Macrophages and T-cells actively contribute to plaque progression and instability (93). In heart failure, the role of metabolism becomes even more pronounced. Cardiomyocytes rely heavily on mitochondrial oxidative metabolism. When mitochondrial efficiency declines, energy supply becomes insufficient to meet physiological demand. This energy deficit contributes directly to contractile dysfunction and disease progression (94, 95).

- Cancer metabolism and immune escape

Cancer represents a highly adaptive immunometabolic system rather than a purely genetic disease (17). Tumor cells reprogram their metabolism to support continuous proliferation. One of the most characteristic changes is the shift toward aerobic glycolysis, even in oxygen-rich environments. This metabolic adaptation is not only for energy production. It also supports biosynthesis and rapid cellular growth. At the same time, it reshapes the tumor microenvironment. Immune cells within tumors are also metabolically reprogrammed (96-99). Competition for nutrients and local accumulation of metabolic by-products impair effective immune responses. This leads to functional exhaustion of cytotoxic immune cells (100). Additionally, inflammatory signaling within the tumor microenvironment does not necessarily eliminate cancer cells. Instead, it can promote survival, angiogenesis, and tissue remodeling. This creates a stable but pathological ecosystem that supports tumor progression and immune escape (101).

- Neurodegeneration and brain energy failure

Neurodegenerative disorders are closely associated with both metabolic failure and chronic neuroinflammation (102, 103). Neurons have high and continuous energy demands, relying primarily on oxidative phosphorylation. Mitochondrial dysfunction can impair synaptic transmission and increase neuronal vulnerability to metabolic stress (104). Microglia play a central role in disease progression. Under stress conditions, they adopt a chronically activated phenotype. This leads to sustained release of inflammatory mediators within the brain microenvironment. Importantly, neuronal injury and immune activation reinforce each other. Energy failure increases vulnerability to inflammation, while chronic inflammation further impairs mitochondrial function and synaptic integrity. In diseases such as Alzheimer's and Parkinson's, this bidirectional loop becomes a major driver of progressive neurodegeneration (102, 105, 106).

- Chronic inflammatory disorders

Chronic inflammatory diseases, including autoimmune conditions, reflect persistent disruption of immunometabolic balance. In these states, immune activation does not return to baseline after an initial trigger. Instead, inflammation becomes self-sustaining (107). Metabolic stress maintains

immune activation, while inflammatory signaling continuously disrupts metabolic regulation. This creates a stable pathological state rather than a transient response. Tissue damage accumulates gradually over time. Depending on the organ involved, this can manifest as fibrosis, functional decline, or systemic symptoms. Importantly, these conditions highlight that inflammation and metabolism are not separate processes. They operate as a single integrated system that can become pathologically locked (108, 109).

Current Challenges and Knowledge Gaps

Despite rapid progress in immunometabolic research, several key limitations still restrict clinical translation. Most of these challenges are not merely technical; they reflect the absence of a sufficiently integrated physiological framework. They reflect the absence of a fully unified physiological framework. A major issue is the lack of integrated system-level models. Most current studies still focus on isolated pathways or single organ systems. This makes it difficult to predict whole-body responses. Immunometabolic reprogramming inherently involves multiple organ systems (110), yet most experimental designs remain reductionist. Another important challenge is biological heterogeneity. Immunometabolic responses vary significantly between individuals. Factors such as age, sex, genetic background, microbiome composition, and comorbidities all influence system behavior. As a result, identical stimuli can produce very different immune and metabolic outcomes (111, 112).

The translational gap between experimental models and human disease is also substantial. Many mechanistic findings are generated in simplified in vitro or animal systems. While these models are useful, they often fail to capture the complexity of human immunometabolic interactions. This limits predictive accuracy in clinical settings (113, 114). Biomarker validation remains another critical barrier. Although many candidate markers have been identified, few have achieved robust clinical validation. Single biomarkers often lack specificity due to overlapping immune and metabolic pathways. Even multi-marker approaches require standardization before widespread clinical adoption (115, 116). Therapeutic specificity is also a major limitation. Many current interventions target broad pathways such as inflammation or metabolism. However, these pathways are deeply interconnected. As a result, interventions may produce unintended effects in non-target tissues. This reduces long-term efficacy and increases variability in patient response. Overall, these challenges highlight the need for more integrated research strategies. A systems-level approach that combines physiology, multi-omics data, and computational modeling is essential to move the field forward.

Future Directions

The field of immunometabolic research is rapidly moving toward more integrated and predictive frameworks. Future progress will depend on shifting from descriptive biology to system-level modeling of disease dynamics. A key direction is systems-level disease modeling. Instead of analyzing isolated pathways, future models will integrate immune, metabolic, and organ-level interactions. These models will aim to capture dynamic behavior over time, including feedback loops and tipping points in disease progression. Another major development is the integration of artificial intelligence with physiological networks. Machine learning approaches can identify hidden patterns across multi-omics and clinical datasets. When combined with mechanistic models, AI can help improve prediction of disease trajectories and treatment response. However, interpretability will remain essential for clinical use. Personalized immunometabolic medicine is also expected to become a central goal. Patients with the same clinical diagnosis often show distinct immunometabolic profiles. Future approaches will stratify patients based on immune–metabolic network signatures rather than broad disease labels. This will support more precise and targeted interventions. Multi-target drug development is another important direction. Given the network nature of immunometabolic dysfunction, single-

target therapies are often insufficient. Future therapeutic development may increasingly focus on coordinated modulation of multiple metabolic, inflammatory, and mitochondrial pathways. Real-time metabolic–immune monitoring represents a further step toward clinical translation. Continuous or near-real-time assessment of metabolic and inflammatory markers could allow dynamic treatment adjustment. This would shift clinical practice from static measurement to adaptive disease management.

Discussion

Immunometabolic reprogramming provides a unifying framework for understanding disease across multiple biological scales. The findings summarized in this review support the concept that immune and metabolic systems are not parallel processes but deeply integrated components of a single regulatory network. This integration becomes particularly evident under conditions of chronic stress, where physiological balance is replaced by stable pathological states. A central insight from current evidence is that disease cannot be fully explained through linear pathway activation. Instead, pathological states emerge from network-level reorganization involving immune signaling, metabolic flux, and organ-level adaptation. This network behavior explains why many diseases share convergent features despite distinct clinical presentations. One of the most important implications of this framework is the reinterpretation of chronic inflammation. Rather than being a localized or self-limiting response, chronic inflammation represents a sustained metabolic state. In this context, inflammatory signaling is not merely a driver of pathology but also a reflection of underlying metabolic instability. This bidirectional relationship creates a feedback loop that stabilizes disease progression. Mitochondrial function emerges as a key determinant in this system. As central hubs of bioenergetics and signaling, mitochondria integrate environmental stress, metabolic demand, and immune activation. When mitochondrial integrity is compromised, both energy production and immune regulation become dysregulated. This positions mitochondria as critical nodes in the transition from physiological adaptation to pathological persistence.

Another important aspect is the heterogeneity of immunometabolic responses across tissues. Organ-specific differences in metabolic demand and immune composition shape distinct disease phenotypes. However, despite this heterogeneity, the underlying principle of coupled immune–metabolic dysfunction remains consistent. This suggests that organ-specific diseases may represent different manifestations of a shared systemic framework. From a translational perspective, these findings suggest that therapeutic durability may depend not only on the potency of individual targets but also on the capacity to restore network stability across metabolic, inflammatory, and mitochondrial compartments. The integration of multi-omics technologies has significantly advanced this field by enabling the characterization of disease states across multiple biological layers. Transcriptomic, proteomic, and metabolomic datasets consistently demonstrate coordinated alterations in immune and metabolic pathways. However, translating these findings into clinically actionable frameworks remains a major challenge. Another critical gap lies in biomarker interpretation. While numerous candidate biomarkers exist, their clinical utility is often limited by contextual variability. The same biomarker can reflect different physiological states depending on metabolic and inflammatory context. This reinforces the need for composite, systems-based biomarker panels rather than single-marker approaches. Overall, the immunometabolic framework shifts the conceptualization of disease from pathway dysfunction to network instability. This shift has profound implications for both basic research and clinical translation. It suggests that future progress will depend on the ability to integrate multi-layer biological data into predictive models that reflect the dynamic nature of disease. Finally, this perspective supports a transition toward precision immunometabolic medicine. Instead of categorizing diseases based solely on clinical phenotype, future approaches will likely rely on underlying network signatures. This may enable

more accurate stratification of patients and more effective therapeutic targeting.

Conclusion

Immunometabolic reprogramming represents a unifying principle in modern disease biology. Across diverse conditions, immune activation and metabolic dysfunction appear tightly coupled. This coupling is not incidental. It reflects a core organizational feature of biological systems under stress. Evidence from molecular studies, multi-omics datasets, and clinical observations consistently supports this integrated view. Disease cannot be fully explained by isolated pathways. It emerges from coordinated dysfunction across immune, metabolic, and organ-level networks. This perspective marks a clear shift from pathway biology toward systems physiology. Instead of focusing on single signaling cascades, the emphasis moves to dynamic interactions between energy homeostasis, inflammatory signaling, and tissue function. Disease is therefore better understood as a state of network imbalance rather than a linear molecular defect. This shift has important implications for therapeutic innovation. Targeting single molecules often produces limited or temporary effects. In contrast, system-level strategies that address multiple interconnected nodes may offer more durable outcomes. This includes combined metabolic and anti-inflammatory approaches, as well as interventions targeting mitochondrial function and cellular energy balance. Finally, immunometabolic reprogramming provides a conceptual foundation for precision medicine. By integrating biomarkers, functional data, and systems-level analysis, it becomes possible to stratify patients based on underlying biological networks rather than broad clinical labels. This approach may ultimately lead to more effective, individualized, and mechanistically guided therapies.

Mechanistic and Translational Relevance

Immunometabolic reprogramming provides a mechanistic framework linking cellular energy sensing, inflammatory signaling, mitochondrial function, and organ-level dysfunction across diverse disease states. At the cellular level, metabolic pathways such as AMPK–mTOR signaling, glycolysis, and oxidative phosphorylation dynamically regulate immune cell activation and functional phenotype, while inflammatory mediators reciprocally reshape substrate utilization, insulin signaling, and mitochondrial activity. Persistent disruption of these interactions establishes self-reinforcing feedback loops involving metabolic stress, oxidative imbalance, and inflammatory signaling, thereby promoting the transition from adaptive responses to chronic pathological states. Mitochondria represent a critical integration node within this network because impaired bioenergetics and excessive reactive oxygen species generation can simultaneously compromise cellular function and amplify inflammatory pathways. From a translational perspective, this integrated model supports therapeutic strategies that move beyond isolated cytokine or metabolic targets toward coordinated modulation of interconnected immunometabolic pathways. AMPK activation, mTOR modulation, restoration of mitochondrial homeostasis, reduction of oxidative stress, and selective control of inflammatory signaling represent potentially complementary therapeutic approaches. Importantly, the network architecture of immunometabolic disease also provides a rationale for combination therapies and biomarker-guided patient stratification. Integrated immune, metabolic, and mitochondrial biomarker profiles may help identify mechanistic disease subtypes, predict therapeutic responsiveness, and support precision immunometabolic interventions. Future integration of multi-omics profiling with computational network modeling may further enable identification of actionable regulatory nodes and dynamic treatment strategies tailored to individual disease states.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interests

The author declares that there is no conflict of interest.

Author Contributions

All authors contributed to the conception and design of the study, literature search, data interpretation, drafting of the manuscript, and critical revision of the article. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethics Statement

All ethical considerations, including plagiarism, data fabrication, and duplicate publication, have been fully observed by the authors.

Acknowledgement

The authors sincerely acknowledge and appreciate all individuals and organizations who contributed to and supported the completion of this work.

Publisher's Note

The graphical abstract was prepared by the journal's editorial team using artificial intelligence-assisted design tools and was reviewed and approved by the authors prior to publication.

Reference

1. Buck MD, Sowell RT, Kaech SM, Pearce EL. Metabolic Instruction of Immunity. Cell. 2017;169(4):570-86. https://doi.org/10.1016/j.cell.2017.04.004.

2. Jung J, Zeng H, Horng T. Metabolism as a guiding force for immunity. Nature cell biology. 2019;21(1):85-93. https://doi.org/10.1038/s41556-018-0217-x.

3. Voss K, Hong HS, Bader JE, Sugiura A, Lyssiotis CA, Rathmell JC. A guide to interrogating immunometabolism. Nature reviews Immunology. 2021;21(10):637-52. https://doi.org/10.1038/s41577-021-00529-8.

4. Pearce EL, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. Immunity. 2013;38(4):633-43. https://doi.org/10.1016/j.immuni.2013.04.005.

5. O'Neill LA, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. Nature reviews Immunology. 2016;16(9):553-65. https://doi.org/10.1038/nri.2016.70.

6. Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nature reviews Genetics. 2011;12(1):56-68. https://doi.org/10.1038/nrg2918.

7. Purohit V, Wagner A, Yosef N, Kuchroo VK. Systems-based approaches to study immunometabolism. Cellular & molecular immunology. 2022;19(3):409-20. https://doi.org/10.1038/s41423-021-00783-9.

8. Yang X. Multitissue Multiomics Systems Biology to Dissect Complex Diseases. Trends in molecular medicine. 2020;26(8):718-28. https://doi.org/10.1016/j.molmed.2020.04.006.

9. Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. Genome biology. 2017;18(1):83. https://doi.org/10.1186/s13059-017-1215-1.

10. Hotamisligil GS. Foundations of Immunometabolism and Implications for Metabolic Health and Disease. Immunity. 2017;47(3):406-20. https://doi.org/10.1016/j.immuni.2017.08.009.

11. Goul C, Peruzzo R, Zoncu R. The molecular basis of nutrient sensing and signalling by mTORC1 in metabolism regulation and disease. Nature reviews Molecular cell biology. 2023;24(12):857-75. https://doi.org/10.1038/s41580-023-00641-8.

12. Hu T, Liu CH, Lei M, Zeng Q, Li L, Tang H, et al. Metabolic regulation of the immune system in health and diseases: mechanisms and interventions. Signal transduction and targeted therapy. 2024;9(1):268. https://doi.org/10.1038/s41392-024-01954-6.

13. Smith TKT, Townsend LK, Smiles WJ, Oakhill JS, Fullerton MD, Steinberg GR. AMPK at the interface of nutrient sensing, metabolic flux and energy homeostasis. Nature metabolism. 2026;8(1):27-51. https://doi.org/10.1038/s42255-025-01442-3.

14. Ma S, Ming Y, Wu J, Cui G. Cellular metabolism regulates the differentiation and function of T-cell subsets. Cellular & molecular immunology. 2024;21(5):419-35. https://doi.org/10.1038/s41423-024-01148-8.

15. Jantz-Naeem N, Guvencli N, Böttcher-Loschinski R, Böttcher M, Mougiakakos D, Kahlfuss S. Metabolic T-cell phenotypes: from bioenergetics to function. American journal of physiology Cell physiology. 2025;328(3):C1062-c75.

https://doi.org/10.1152/ajpcell.00478.2024.
16. Mirchandani AS, Sanchez-Garcia MA, Walmsley SR. How oxygenation shapes immune responses: emerging roles for physioxia and pathological hypoxia. Nature reviews Immunology. 2025;25(3):161-77. https://doi.org/10.1038/s41577-024-01087-5.
17. De Martino M, Rathmell JC, Galluzzi L, Vanpouille-Box C. Cancer cell metabolism and antitumour immunity. Nature reviews Immunology. 2024;24(9):654-69. https://doi.org/10.1038/s41577-024-01026-4.
18. Tilg H, Ianiro G, Gasbarrini A, Adolph TE. Adipokines: masterminds of metabolic inflammation. Nature reviews Immunology. 2025;25(4):250-65. https://doi.org/10.1038/s41577-024-01103-8.
19. De Baat A, Trinh B, Ellingsgaard H, Donath MY. Physiological role of cytokines in the regulation of mammalian metabolism. Trends in immunology. 2023;44(8):613-27. https://doi.org/10.1016/j.it.2023.06.002.
20. Chandrasekaran P, Weiskirchen R. Cellular and Molecular Mechanisms of Insulin Resistance. Current Tissue Microenvironment Reports. 2024;5(3):79-90. https://doi.org/10.1007/s43152-024-00056-3.
21. Guo Q, Jin Y, Chen X, Ye X, Shen X, Lin M, et al. NF-κB in biology and targeted therapy: new insights and translational implications. Signal transduction and targeted therapy. 2024;9(1):53. https://doi.org/10.1038/s41392-024-01757-9.
22. Yan S, Santoro A, Niphakis MJ, Pinto AM, Jacobs CL, Ahmad R, et al. Inflammation causes insulin resistance in mice via interferon regulatory factor 3 (IRF3)-mediated reduction in FAHFA levels. Nature communications. 2024;15(1):4605. https://doi.org/10.1038/s41467-024-48220-5.
23. Kwong AC, Ordovas-Montanes J. Deconstructing inflammatory memory across tissue set points using cell circuit motifs. The Journal of allergy and clinical immunology. 2024;154(5):1095-105. https://doi.org/10.1016/j.jaci.2024.09.014.
24. Soták M, Clark M, Suur BE, Börgeson E. Inflammation and resolution in obesity. Nature reviews Endocrinology. 2025;21(1):45-61. https://doi.org/10.1038/s41574-024-01047-y.
25. Auger JP, Zimmermann M, Faas M, Stifel U, Chambers D, Krishnacoumar B, et al. Metabolic rewiring promotes anti-inflammatory effects of glucocorticoids. Nature. 2024;629(8010):184-92. https://doi.org/10.1038/s41586-024-07282-7.
26. Meizlish ML, Franklin RA, Zhou X, Medzhitov R. Tissue Homeostasis and Inflammation. Annual review of immunology. 2021;39:557-81. https://doi.org/10.1146/annurev-immunol-061020-053734.
27. Tarasenko TN, McGuire PJ. The liver is a metabolic and immunologic organ: A reconsideration of metabolic decompensation due to infection in inborn errors of metabolism (IEM). Molecular genetics and metabolism. 2017;121(4):283-8. https://doi.org/10.1016/j.ymgme.2017.06.010.
28. Ehlting C, Wolf SD, Bode JG. Acute-phase protein synthesis: a key feature of innate immune functions of the liver. Biological chemistry. 2021;402(9):1129-45. https://doi.org/10.1515/hsz-2021-0209.
29. Groeger M, Matsuo K, Heidary Arash E, Pereira A, Le Guillou D, Pino C, et al. Modeling and therapeutic targeting of inflammation-induced hepatic insulin resistance using human iPSC-derived hepatocytes and macrophages. Nature communications. 2023;14(1):3902. https://doi.org/10.1038/s41467-023-39311-w.
30. Schwärzler J, Grabherr F, Grander C, Adolph TE, Tilg H. The pathophysiology of MASLD: an immunometabolic perspective. Expert review of clinical immunology. 2024;20(4):375-86. https://doi.org/10.1080/1744666x.2023.2294046.
31. Uehara K, Santoleri D, Whitlock AEG, Titchenell PM. Insulin Regulation of Hepatic Lipid Homeostasis. Comprehensive Physiology. 2023;13(3):4785-809. https://doi.org/10.1002/cphy.c220015.
32. Gallego-Durán R, Hadjihambi A, Ampuero J, Rose CF, Jalan R, Romero-Gómez M. Ammonia-induced stress response in liver disease progression and hepatic encephalopathy. Nature reviews Gastroenterology & hepatology. 2024;21(11):774-91. https://doi.org/10.1038/s41575-024-00970-9.
33. Chait A, den Hartigh LJ. Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease. Frontiers in cardiovascular medicine. 2020;7:22. https://doi.org/10.3389/fcvm.2020.00022.
34. Jacks RD, Lumeng CN. Macrophage and T cell networks in adipose tissue. Nature reviews Endocrinology. 2024;20(1):50-61.

https://doi.org/10.1038/s41574-023-00908-2.
35. Jaitin DA, Adlung L, Thaiss CA, Weiner A, Li B, Descamps H, et al. Lipid-Associated Macrophages Control Metabolic Homeostasis in a Trem2-Dependent Manner. Cell. 2019;178(3):686-98.e14.
https://doi.org/10.1016/j.cell.2019.05.054.
36. Cunnane SC, Trushina E, Morland C, Prigione A, Casadesus G, Andrews ZB, et al. Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing. Nature reviews Drug discovery. 2020;19(9):609-33.
https://doi.org/10.1038/s41573-020-0072-x.
37. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nature reviews Neurology. 2021;17(3):157-72.
https://doi.org/10.1038/s41582-020-00435-y.
38. Monsorno K, Ginggen K, Ivanov A, Buckinx A, Lalive AL, Tchenio A, et al. Loss of microglial MCT4 leads to defective synaptic pruning and anxiety-like behavior in mice. Nature communications. 2023;14(1):5749.
https://doi.org/10.1038/s41467-023-41502-4.
39. Wei Y, Miao Q, Zhang Q, Mao S, Li M, Xu X, et al. Aerobic glycolysis is the predominant means of glucose metabolism in neuronal somata, which protects against oxidative damage. Nature neuroscience. 2023;26(12):2081-9.
https://doi.org/10.1038/s41593-023-01476-4.
40. Picca A, Calvani R, Coelho-Junior HJ, Landi F, Bernabei R, Marzetti E. Mitochondrial Dysfunction, Oxidative Stress, and Neuroinflammation: Intertwined Roads to Neurodegeneration. Antioxidants (Basel, Switzerland). 2020;9(8).
https://doi.org/10.3390/antiox9080647.
41. Pasut A, Lama E, Van Craenenbroeck AH, Kroon J, Carmeliet P. Endothelial cell metabolism in cardiovascular physiology and disease. Nature reviews Cardiology. 2025;22(12):923-43.
https://doi.org/10.1038/s41569-025-01162-x.
42. Liu C, Lei S, Cai T, Cheng Y, Bai J, Fu W, et al. Inducible nitric oxide synthase activity mediates TNF-α-induced endothelial cell dysfunction. American journal of physiology Cell physiology. 2023;325(3):C780-c95.
https://doi.org/10.1152/ajpcell.00153.2023.
43. Lehners M, Schmidt H, Zaldivia MTK, Stehle D, Krämer M, Peter A, et al. Single-cell analysis identifies the CNP/GC-B/cGMP axis as marker and regulator of modulated VSMCs in atherosclerosis. Nature communications. 2025;16(1):429.
https://doi.org/10.1038/s41467-024-55687-9.
44. Yu L, Xu L, Chu H, Peng J, Sacharidou A, Hsieh HH, et al. Macrophage-to-endothelial cell crosstalk by the cholesterol metabolite 27HC promotes atherosclerosis in male mice. Nature communications. 2023;14(1):4101.
https://doi.org/10.1038/s41467-023-39586-z.
45. Marques E, Kramer R, Ryan DG. Multifaceted mitochondria in innate immunity. npj metabolic health and disease. 2024;2(1):6.
https://doi.org/10.1038/s44324-024-00008-3.
46. Bennett CF, Ronayne CT, Puigserver P. Targeting adaptive cellular responses to mitochondrial bioenergetic deficiencies in human disease. The FEBS journal. 2022;289(22):6969-93.
https://doi.org/10.1111/febs.16195.
47. Koren SA, Ahmed Selim N, De la Rosa L, Horn J, Farooqi MA, Wei AY, et al. All-optical spatiotemporal mapping of ROS dynamics across mitochondrial microdomains in situ. Nature communications. 2023;14(1):6036.
https://doi.org/10.1038/s41467-023-41682-z.
48. Sutandy FXR, Gößner I, Tascher G, Münch C. A cytosolic surveillance mechanism activates the mitochondrial UPR. Nature. 2023;618(7966):849-54.
https://doi.org/10.1038/s41586-023-06142-0.
49. Billingham LK, Stoolman JS, Vasan K, Rodriguez AE, Poor TA, Szibor M, et al. Mitochondrial electron transport chain is necessary for NLRP3 inflammasome activation. Nature immunology. 2022;23(5):692-704.
https://doi.org/10.1038/s41590-022-01185-3.
50. Próchnicki T, Vasconcelos MB, Robinson KS, Mangan MSJ, De Graaf D, Shkarina K, et al. Mitochondrial damage activates the NLRP10 inflammasome. Nature immunology. 2023;24(4):595-603.
https://doi.org/10.1038/s41590-023-01451-y.
51. Wu H, Zhao X, Hochrein SM, Eckstein M, Gubert GF, Knöpper K, et al. Mitochondrial dysfunction promotes the transition of precursor to terminally exhausted T cells through HIF-1α-mediated glycolytic reprogramming. Nature communications. 2023;14(1):6858.
https://doi.org/10.1038/s41467-023-42634-3.
52. Marchi S, Guilbaud E, Tait SWG, Yamazaki T, Galluzzi L. Mitochondrial control of inflammation. Nature reviews Immunology. 2023;23(3):159-73.
https://doi.org/10.1038/s41577-022-00760-x.
53. Zong Y, Li H, Liao P, Chen L, Pan Y, Zheng Y, et al. Mitochondrial dysfunction: mechanisms and

advances in therapy. Signal transduction and targeted therapy. 2024;9(1):124. https://doi.org/10.1038/s41392-024-01839-8.
54. Mogilenko DA, Sergushichev A, Artyomov MN. Systems Immunology Approaches to Metabolism. Annual review of immunology. 2023;41:317-42. https://doi.org/10.1146/annurev-immunol-101220-031513.
55. Chen HJ, Sévin DC, Griffith GR, Vappiani J, Booty LM, van Roomen C, et al. Integrated metabolic-transcriptomic network identifies immunometabolic modulations in human macrophages. Cell reports. 2024;43(9):114741. https://doi.org/10.1016/j.celrep.2024.114741.
56. Ting KKY. Revisiting the role of hypoxia-inducible factors and nuclear factor erythroid 2-related factor 2 in regulating macrophage inflammation and metabolism. Frontiers in cellular and infection microbiology. 2024;14:1403915. https://doi.org/10.3389/fcimb.2024.1403915.
57. Sabogal-Guáqueta AM, Marmolejo-Garza A, Trombetta-Lima M, Oun A, Hunneman J, Chen T, et al. Species-specific metabolic reprogramming in human and mouse microglia during inflammatory pathway induction. Nature communications. 2023;14(1):6454. https://doi.org/10.1038/s41467-023-42096-7.
58. Fu J, Zhu F, Xu CJ, Li Y. Metabolomics meets systems immunology. EMBO reports. 2023;24(4):e55747. https://doi.org/10.15252/embr.202255747.
59. Ogger PP, Murray PJ. Dissecting inflammation in the immunemetabolomic era. Cellular and molecular life sciences : CMLS. 2025;82(1):182. https://doi.org/10.1007/s00018-025-05715-8.
60. Foretz M, Guigas B, Viollet B. Metformin: update on mechanisms of action and repurposing potential. Nature reviews Endocrinology. 2023;19(8):460-76. https://doi.org/10.1038/s41574-023-00833-4.
61. Nojima I, Wada J. Metformin and Its Immune-Mediated Effects in Various Diseases. International journal of molecular sciences. 2023;24(1). https://doi.org/10.3390/ijms24010755.
62. Viollet B. The Energy Sensor AMPK: Adaptations to Exercise, Nutritional and Hormonal Signals. In: Spiegelman B, editor. Hormones, Metabolism and the Benefits of Exercise. Cham (CH): Springer Copyright 2017, The Author(s). 2017. p. 13-24.

https://doi.org/10.1007/978-3-319-72790-5_2.
63. Saxton RA, Sabatini DM. mTOR Signaling in Growth, Metabolism, and Disease. Cell. 2017;168(6):960-76. https://doi.org/10.1016/j.cell.2017.02.004.
64. Lin H, Ao H, Guo G, Liu M. The Role and Mechanism of Metformin in Inflammatory Diseases. Journal of inflammation research. 2023;16:5545-64. https://doi.org/10.2147/jir.s436147.
65. Gokani V, Kotta A, Repaka V, Rauniyar S, Noch EK. Targeting Metabolic Vulnerabilities in Glioblastoma: a Framework for Multi-node Combination Therapy. Current Oncology Reports. 2026;28(1):19. https://doi.org/10.1007/s11912-026-01746-x.
66. He B, Lu C, Zheng G, He X, Wang M, Chen G, et al. Combination therapeutics in complex diseases. Journal of cellular and molecular medicine. 2016;20(12):2231-40. https://doi.org/10.1111/jcmm.12930.
67. Tabas I, Glass CK. Anti-Inflammatory Therapy in Chronic Disease: Challenges and Opportunities. Science (New York, NY). 2013;339(6116):166-72. https://doi.org/10.1126/science.1230720.
68. Ahn AC, Tewari M, Poon CS, Phillips RS. The limits of reductionism in medicine: could systems biology offer an alternative? PLoS medicine. 2006;3(6):e208. https://doi.org/10.1371/journal.pmed.0030208.
69. Kitano H. Systems biology: a brief overview. Science (New York, NY). 2002;295(5560):1662-4. https://doi.org/10.1126/science.1069492.
70. Hood L, Flores M. A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory. New biotechnology. 2012;29(6):613-24. https://doi.org/10.1016/j.nbt.2012.03.004.
71. Wishart DS. Emerging applications of metabolomics in drug discovery and precision medicine. Nature reviews Drug discovery. 2016;15(7):473-84. https://doi.org/10.1038/nrd.2016.32.
72. Subramanian I, Verma S, Kumar S, Jere A, Anamika K. Multi-omics Data Integration, Interpretation, and Its Application. Bioinformatics and biology insights. 2020;14:1177932219899051. https://doi.org/10.1177/1177932219899051.
73. Pietzner M, Kaul A, Henning AK, Kastenmüller G, Artati A, Lerch MM, et al. Comprehensive metabolic profiling of chronic low-grade

inflammation among generally healthy individuals. BMC medicine. 2017;15(1):210.
https://doi.org/10.1186/s12916-017-0974-6.

74. Zheng Z, Yin X, Liu J, Zhang Y. Triglyceride-glucose index and its derivatives as emerging biomarkers of insulin resistance for prognostic evaluation of cardiovascular-kidney-metabolic syndrome: mechanisms and clinical applications. Frontiers in pharmacology. 2026;17:1787130.
https://doi.org/10.3389/fphar.2026.1787130

75. Picca A, Guerra F, Calvani R, Bucci C, Lo Monaco MR, Bentivoglio AR, et al. Mitochondrial Dysfunction and Aging: Insights from the Analysis of Extracellular Vesicles. International journal of molecular sciences. 2019;20(4).
https://doi.org/10.3390/ijms20040805

76. Adepoju A, Adepoju D. Biomarker Discovery in Clinical Biology Enhances Early Disease Detection, Prognosis, and Personalized Treatment Strategies. 2025;02:229-52.
https://doi.org/10.5281/zenodo.15244690.

77. Méndez Hernández R, Ramasco Rueda F. Biomarkers as Prognostic Predictors and Therapeutic Guide in Critically Ill Patients: Clinical Evidence. Journal of Personalized Medicine. 2023;13(2):333.
https://doi.org/10.3390/jpm13020333.

78. Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. Nature Reviews Drug Discovery. 2007;6(4):287-93.
https://doi.org/10.1038/nrd2251.

79. Liu R, Wang X, Aihara K, Chen L. Early diagnosis of complex diseases by molecular biomarkers, network biomarkers, and dynamical network biomarkers. Medicinal research reviews. 2014;34(3):455-78.
https://doi.org/10.1002/med.21293.

80. Shanthamallu US, Kilpatrick C, Jones A, Rubin J, Saleh A, Barabási AL, et al. A Network-Based Framework to Discover Treatment-Response-Predicting Biomarkers for Complex Diseases. The Journal of molecular diagnostics : JMD. 2024;26(10):917-30.
https://doi.org/10.1016/j.jmoldx.2024.06.008.

81. Makowski L, Chaib M, Rathmell JC. Immunometabolism: From basic mechanisms to translation. Immunological reviews. 2020;295(1):5-14.
https://doi.org/10.1111/imr.12858.

82. SantaCruz-Calvo S, Bharath L, Pugh G, SantaCruz-Calvo L, Lenin RR, Lutshumba J, et al. Adaptive immune cells shape obesity-associated type 2 diabetes mellitus and less prominent comorbidities. Nature reviews Endocrinology. 2022;18(1):23-42.
https://doi.org/10.1038/s41574-021-00575-1.

83. Minihane AM, Vinoy S, Russell WR, Baka A, Roche HM, Tuohy KM, et al. Low-grade inflammation, diet composition and health: current research evidence and its translation. The British journal of nutrition. 2015;114(7):999-1012.
https://doi.org/10.1017/s0007114515002093.

84. Mirabelli M, Misiti R, Sicilia L, Brunetti FS, Chiefari E, Brunetti A, et al. Hypoxia in Human Obesity: New Insights from Inflammation towards Insulin Resistance-A Narrative Review. International journal of molecular sciences. 2024;25(18).
https://doi.org/10.3390/ijms25189802.

85. Bo T, Gao L, Yao Z, Shao S, Wang X, Proud CG, et al. Hepatic selective insulin resistance at the intersection of insulin signaling and metabolic dysfunction-associated steatotic liver disease. Cell metabolism. 2024;36(5):947-68.
https://doi.org/10.1016/j.cmet.2024.04.006.

86. Kumar S, Elmansi A, Noureldein M, Harper J. Editorial: The crosstalk between metabolism and inflammation in aging and longevity. Frontiers in endocrinology. 2025;16:1734527.
https://doi.org/10.3389/fendo.2025.1734527.

87. Luo Y, Lin H. Inflammation initiates a vicious cycle between obesity and nonalcoholic fatty liver disease. Immunity, inflammation and disease. 2021;9(1):59-73.
https://doi.org/10.1002/iid3.391.

88. Thimmappa PY, Vasishta S, Ganesh K, Nair AS, Joshi MB. Neutrophil (dys)function due to altered immuno-metabolic axis in type 2 diabetes: implications in combating infections. Human cell. 2023;36(4):1265-82.
https://doi.org/10.1007/s13577-023-00905-7.

89. Fleetwood AJ, Noonan J, La Gruta N, Kallies A, Murphy AJ. Immunometabolism in atherosclerotic disorders. Nature cardiovascular research. 2024;3(6):637-50.
https://doi.org/10.1038/s44161-024-00473-5.

90. Mohanta SK, Heron C, Klaus-Bergmann A, Horstmann H, Brakenhielm E, Giannarelli C, et al. Metabolic and Immune Crosstalk in Cardiovascular Disease. Circulation research. 2025;136(11):1433-53.

https://doi.org/10.1161/circresaha.125.325496.
91. Pacinella G, Ciaccio AM, Tuttolomondo A. Endothelial Dysfunction and Chronic Inflammation: The Cornerstones of Vascular Alterations in Age-Related Diseases. International journal of molecular sciences. 2022;23(24). https://doi.org/10.3390/ijms232415722.
92. Xue C, Chen K, Gao Z, Bao T, Dong L, Zhao L, et al. Common mechanisms underlying diabetic vascular complications: focus on the interaction of metabolic disorders, immuno-inflammation, and endothelial dysfunction. Cell communication and signaling : CCS. 2023;21(1):298. https://doi.org/10.1186/s12964-022-01016-w.
93. Malekmohammad K, Bezsonov EE, Rafieian-Kopaei M. Role of Lipid Accumulation and Inflammation in Atherosclerosis: Focus on Molecular and Cellular Mechanisms. Frontiers in cardiovascular medicine. 2021;8:707529. https://doi.org/10.3389/fcvm.2021.707529.
94. Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac Energy Metabolism in Heart Failure. Circulation research. 2021;128(10):1487-513. https://doi.org/10.1161/circresaha.121.318241.
95. Zhou B, Tian R. Mitochondrial dysfunction in pathophysiology of heart failure. The Journal of clinical investigation. 2018;128(9):3716-26. https://doi.org/10.1172/jci120849.
96. Cai H, Zhang F, Xu F, Yang C. Metabolic reprogramming and therapeutic targeting in non-small cell lung cancer: emerging insights beyond the Warburg effect. Frontiers in oncology. 2025;15:1564226. https://doi.org/10.3389/fonc.2025.1564226.
97. Jiang M, Fang H, Tian H. Metabolism of cancer cells and immune cells in the initiation, progression, and metastasis of cancer. Theranostics. 2025;15(1):155-88. https://doi.org/10.7150/thno.103376.
98. Lunt SY, Vander Heiden MG. Aerobic glycolysis: meeting the metabolic requirements of cell proliferation. Annual review of cell and developmental biology. 2011;27:441-64. https://doi.org/10.1146/annurev-cellbio-092910-154237.
99. Zhang H, Li S, Wang D, Liu S, Xiao T, Gu W, et al. Metabolic reprogramming and immune evasion: the interplay in the tumor microenvironment. Biomarker research. 2024;12(1):96. https://doi.org/10.1186/s40364-024-00646-1.
100. Kouidhi S, Ben Ayed F, Benammar Elgaaied A. Targeting Tumor Metabolism: A New Challenge to Improve Immunotherapy. Frontiers in immunology. 2018;9:353. https://doi.org/10.3389/fimmu.2018.00353.
101. Greten FR, Grivennikov SI. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. Immunity. 2019;51(1):27-41. https://doi.org/10.1016/j.immuni.2019.06.025.
102. Adamu A, Li S, Gao F, Xue G. The role of neuroinflammation in neurodegenerative diseases: current understanding and future therapeutic targets. Frontiers in aging neuroscience. 2024;16:1347987. https://doi.org/10.3389/fnagi.2024.1347987.
103. van Dijk G, van Heijningen S, Reijne AC, Nyakas C, van der Zee EA, Eisel UL. Integrative neurobiology of metabolic diseases, neuroinflammation, and neurodegeneration. Frontiers in neuroscience. 2015;9:173. https://doi.org/10.3389/fnins.2015.00173.
104. Li S, Sheng ZH. Energy matters: presynaptic metabolism and the maintenance of synaptic transmission. Nature reviews Neuroscience. 2022;23(1):4-22. https://doi.org/10.1038/s41583-021-00535-8.
105. Walker FR, Nilsson M, Jones K. Acute and chronic stress-induced disturbances of microglial plasticity, phenotype and function. Current drug targets. 2013;14(11):1262-76. https://doi.org/10.2174/13894501113149990208.
106. Woodburn SC, Bollinger JL, Wohleb ES. The semantics of microglia activation: neuroinflammation, homeostasis, and stress. Journal of neuroinflammation. 2021;18(1):258. https://doi.org/10.1186/s12974-021-02309-6.
107. Blanco LP, Kaplan MJ. Metabolic alterations of the immune system in the pathogenesis of autoimmune diseases. PLoS biology. 2023;21(4):e3002084. https://doi.org/10.1371/journal.pbio.3002084.
108. Kominsky DJ, Campbell EL, Colgan SP. Metabolic shifts in immunity and inflammation. Journal of immunology (Baltimore, Md : 1950). 2010;184(8):4062-8. https://doi.org/10.4049/jimmunol.0903002.
109. Próchnicki T, Latz E. Inflammasomes on the Crossroads of Innate Immune Recognition and Metabolic Control. Cell metabolism. 2017;26(1):71-93. https://doi.org/10.1016/j.cmet.2017.06.018.
110. Subramaniyan P, Parthiban V. The bio-intelligence circuit: a hypothesis-generating

systems framework linking mitochondrial stress, innate immune signaling, and autonomic regulation in chronic inflammation. Frontiers in immunology. 2026;17:1750974. https://doi.org/10.3389/fimmu.2026.1750974.

111. Caldarelli M, Rio P, Marrone A, Giambra V, Gasbarrini A, Gambassi G, et al. Inflammaging: The Next Challenge-Exploring the Role of Gut Microbiota, Environmental Factors, and Sex Differences. Biomedicines. 2024;12(8). https://doi.org/10.3390/biomedicines12081716.

112. De Sanctis JB, Balda Noria G, García AH. Exploring How Adipose Tissue, Obesity, and Gender Influence the Immune Response to Vaccines: A Comprehensive Narrative Review. International journal of molecular sciences. 2025 Jan 20;26(2):862. https://doi.org/10.3390/ijms26020862.

113. Frangogiannis NG. Why animal model studies are lost in translation. The journal of cardiovascular aging. 2022;2(2). https://doi.org/10.20517/jca.2022.10.

114. McGonigle P, Ruggeri B. Animal models of human disease: challenges in enabling translation. Biochemical pharmacology. 2014;87(1):162-71. https://doi.org/10.1016/j.bcp.2013.08.006

115. Quezada H, Guzmán-Ortiz AL, Díaz-Sánchez H, Valle-Rios R, Aguirre-Hernández J. Omics-based biomarkers: current status and potential use in the clinic. Boletin medico del Hospital Infantil de Mexico. 2017;74(3):219-26. https://doi.org/10.1016/j.bmhimx.2017.03.003.

116. Sarkar S, Elliott EC, Henry HR, Ludovico ID, Melchior JT, Frazer-Abel A, et al. Systematic review of type 1 diabetes biomarkers reveals regulation in circulating proteins related to complement, lipid metabolism, and immune response. Clinical proteomics. 2023;20(1):38.

https://doi.org/10.1186/s12014-023-09429-6.