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The Role of Macrophage Metabolic Reprogramming in Regulating Chronic Inflammation and Disease Progression

Ali Mansouri
Organizational affiliation: Bachelor of Laboratory Science, Arak University of Medical Sciences, Delijan Healthcare Network, Arak, Iran

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ABSTRACT

Macrophages, as central components of the innate immune system, play a pivotal role in orchestrating inflammatory responses. Recent evidence highlights that macrophage function is closely governed by metabolic reprogramming, a process in which shifts in cellular metabolism modulate immune phenotypes and effector functions. During chronic inflammation, macrophages exhibit altered utilization of glycolysis, oxidative phosphorylation (OXPHOS), fatty acid oxidation, and glutamine metabolism. These metabolic shifts determine the polarization state of macrophages, driving pro-inflammatory (M1-like) or anti-inflammatory (M2-like) phenotypes. Persistent metabolic dysregulation contributes to uncontrolled inflammation and tissue damage in chronic diseases such as atherosclerosis, diabetes, rheumatoid arthritis, and cancer. In atherosclerosis, macrophages accumulate lipids and undergo metabolic stress that sustains inflammatory activation. In diabetes, hyperglycemia-induced metabolic reprogramming enhances macrophage glycolysis and inflammatory cytokine production. In tumors, the hypoxic microenvironment reshapes macrophage metabolism to support immunosuppressive and pro-tumorigenic activity. Understanding how metabolic pathways regulate macrophage function reveals therapeutic opportunities. Targeting key enzymes such as hexokinase 2, isocitrate dehydrogenase, or AMP-activated protein kinase (AMPK) offers potential to reprogram macrophages toward inflammation resolution. This review integrates findings from immunometabolism and pathophysiology to demonstrate that macrophage metabolic reprogramming acts as a central mechanism linking cellular metabolism to chronic inflammation and disease progression. Therapeutic strategies that correct macrophage metabolic imbalance may provide novel approaches for managing chronic inflammatory disorders and improving patient outcomes.

Introduction

Macrophages are highly plastic immune cells that serve as critical regulators of both innate and adaptive immunity [1]. They are widely recognized for their ability to sense, respond to, and orchestrate immune responses against pathogens, tissue injury, and environmental stressors. Beyond their classical roles in pathogen clearance and antigen presentation, macrophages are now understood to be central modulators of tissue homeostasis, inflammation resolution, and repair processes [2].

In recent years, a growing body of research has illuminated the complex relationship between macrophage function and cellular metabolism, giving rise to the field of immunometabolism. Immunometabolism describes the intricate ways in which metabolic pathways within immune cells influence their activation [3], polarization, and

Corresponding Author:* ***Ali Mansouri* *(alimansouri7697@gmail.com - ORCID: 0009-0000-5988-1445)*

effector functions. Central to this concept is metabolic reprogramming, whereby macrophages adjust their bioenergetics and biosynthetic programs in response to environmental cues, inflammatory signals, or pathogenic stimuli [4].

Macrophages can adopt diverse functional phenotypes, broadly categorized into classically activated (M1-like) pro-inflammatory and alternatively activated (M2-like) anti-inflammatory states. This polarization is not fixed but represents a continuum influenced by cytokines, chemokines, cellular stressors, and metabolic signals. For example, interferon-gamma (IFN-γ) and lipopolysaccharide (LPS) drive M1-like activation, promoting production of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and reactive oxygen species (ROS). Conversely, interleukin-4 (IL-4) and interleukin-13 (IL-13) induce M2-like macrophages, which facilitate tissue repair, wound healing, and the resolution of inflammation through secretion of anti-inflammatory cytokines like IL-10 and transforming growth factor-beta (TGF-β) [5].

Crucially, emerging evidence shows that these functional states are closely linked to distinct metabolic profiles. M1 macrophages rely predominantly on aerobic glycolysis, a phenomenon reminiscent of the Warburg effect observed in tumor cells, whereas M2 macrophages preferentially utilize oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) to generate ATP efficiently. These metabolic programs not only supply energy but also produce intermediates that act as signaling molecules, influencing gene expression and cellular behavior [6].

The importance of macrophage metabolic reprogramming extends beyond acute immune responses, as it plays a central role in chronic inflammation. Chronic inflammation is a sustained, low-grade immune response that contributes to the pathogenesis of a wide range of diseases, including cardiovascular disease, metabolic disorders, neurodegenerative diseases, autoimmune conditions, and cancer [7].

In these contexts, macrophages frequently display dysregulated metabolism, leading to persistent activation, uncontrolled cytokine release, and tissue damage. For instance, in atherosclerotic plaques, macrophages engulf oxidized low-density lipoproteins (oxLDL), transforming into foam cells. These foam cells exhibit impaired mitochondrial function and elevated glycolysis, which perpetuates inflammatory signaling and contributes to plaque instability [8].

Similarly, in obesity-associated diabetes, macrophages in adipose tissue undergo metabolic shifts that enhance glycolysis and ROS production, promoting insulin resistance and chronic metabolic inflammation. In tumors, the hypoxic and nutrient-deprived microenvironment reprograms tumor-associated macrophages (TAMs) toward an immunosuppressive phenotype, supporting angiogenesis, tumor growth, and metastasis [9].

A growing number of studies indicate that specific metabolic pathways govern macrophage responses at multiple levels. Key regulatory nodes include glycolysis, the tricarboxylic acid (TCA) cycle, oxidative phosphorylation, fatty acid metabolism, and amino acid utilization [10].

Glycolytic intermediates, such as glucose-6-phosphate, serve as precursors for nucleotide and lipid biosynthesis, while TCA cycle metabolites like succinate and fumarate can act as signaling molecules to stabilize hypoxia-inducible factor 1-alpha (HIF-1α) and modulate inflammatory gene transcription. Additionally, fatty acid oxidation fuels anti-inflammatory macrophage functions, supporting tissue repair and promoting the resolution of inflammation. These metabolic pathways are interconnected with intracellular signaling networks, including mTOR, AMPK, and NF-κB pathways, creating a complex regulatory landscape in which metabolism and immune function are inextricably linked [11].

Therapeutic targeting of macrophage metabolism has emerged as a promising strategy for managing chronic inflammatory diseases. By modulating key enzymes and signaling nodes, it is possible to shift macrophages toward a resolving or anti-inflammatory phenotype, reducing tissue damage and improving clinical outcomes. For example, pharmacological activation of AMP-activated protein kinase (AMPK) enhances FAO and OXPHOS, promoting anti-inflammatory responses in metabolic disorders [12].

Inhibition of glycolysis or selective modulation of glutamine metabolism has been shown to reduce pro-inflammatory activation in macrophages within atherosclerotic plaques or tumor microenvironments. Nutritional interventions, including omega-3 fatty acids, ketone bodies, or caloric restriction, may also modulate macrophage metabolism and attenuate chronic inflammation. Moreover, advanced techniques such as single-cell metabolomics, flux analysis, and spatial transcriptomics enable high-resolution mapping of metabolic heterogeneity within macrophage populations, offering opportunities for precision immunometabolic therapies [13].

Despite significant progress, many challenges remain. The dynamic and context-dependent nature of macrophage metabolism means that interventions must be carefully tailored to disease type, stage, and tissue microenvironment. Moreover, systemic metabolic modulation may affect other cell types, necessitating strategies for targeted delivery.

Understanding how macrophage metabolism interacts with other components of the immune system, including T cells, dendritic cells, and stromal cells, remains an active area of research. Future studies integrating metabolic, transcriptomic, and proteomic data will be essential to fully elucidate the mechanisms by which metabolic reprogramming shapes macrophage function and drives chronic disease progression [14].

In conclusion, macrophage metabolic reprogramming represents a central mechanism linking cellular metabolism to immune function, chronic inflammation, and disease pathogenesis. By deciphering the metabolic cues that govern macrophage activation, researchers can uncover novel therapeutic targets and design strategies to restore immune balance, prevent tissue damage, and improve patient outcomes across a range of chronic inflammatory diseases [15].

The intersection of metabolism and immunity thus offers profound insights into disease mechanisms and a transformative framework for the development of next-generation immunotherapies. In figure (1), The Role of Macrophage Metabolic Reprogramming in Regulating Chronic Inflammation and Disease Progression was illustrated [16].

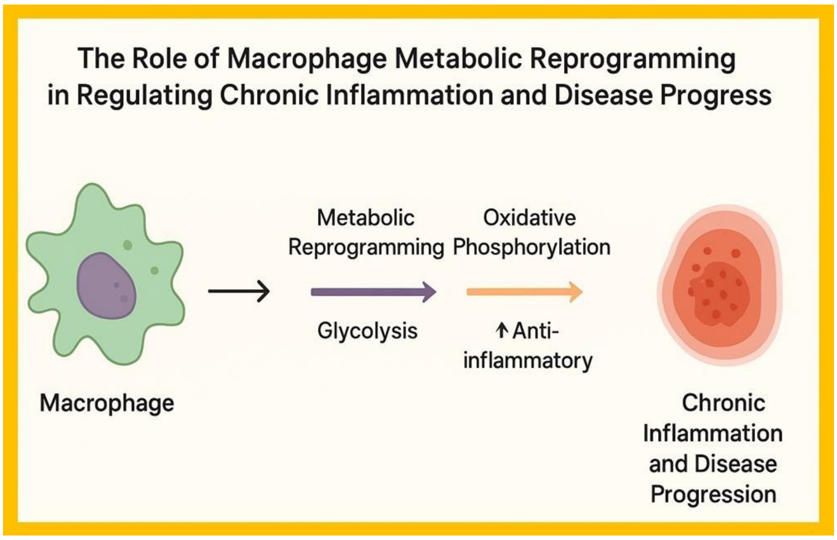

Figure 1. The Role of Macrophage Metabolic Reprogramming in Regulating Chronic Inflammation and Disease Progression

Background

Macrophages are pivotal cells in the innate immune system, playing essential roles in pathogen clearance, tissue homeostasis, and immune regulation [17-19].

Their functional versatility allows them to adapt to various microenvironments, a phenomenon known as macrophage plasticity. This adaptability is not only a response to external stimuli but is also intricately linked to their metabolic state. The concept of "macrophage metabolic reprogramming" has emerged as a central theme in understanding how metabolic pathways influence macrophage function and, consequently, the progression of chronic inflammatory diseases [20].

Macrophage Polarization and Metabolic States

Macrophages can adopt distinct functional phenotypes, primarily classified into classically activated (M1) and alternatively activated (M2) macrophages. M1 macrophages are typically induced by pro-inflammatory stimuli such as lipopolysaccharide (LPS) and interferon-gamma (IFN-γ). They are characterized by high glycolytic activity, producing large amounts of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, as well as reactive oxygen species (ROS). This metabolic shift towards glycolysis, even in the presence of oxygen, is reminiscent of the Warburg effect observed in cancer cells and is essential for the rapid energy production required during acute inflammation [21].

In contrast, M2 macrophages are induced by anti-inflammatory cytokines such as IL-4 and IL-13. They exhibit enhanced oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO), processes that support tissue repair, wound healing, and resolution of inflammation. The metabolic pathways in M2 macrophages are geared towards energy efficiency and the production of anti-inflammatory cytokines like IL-10 and TGF-β [22].

The balance between M1 and M2 macrophage polarization is not merely a functional dichotomy but is deeply rooted in metabolic pathways. The metabolic environment dictates the activation of specific transcription factors and signaling pathways that drive macrophage polarization. For instance, hypoxia-inducible factor 1-alpha (HIF-1α) promotes glycolytic gene expression in M1 macrophages, while peroxisome proliferator-activated receptor gamma (PPAR-γ) and liver X receptors (LXRs) are involved in the metabolic reprogramming of M2 macrophages [23].

Macrophage Metabolic Reprogramming in Chronic Inflammation

Chronic inflammation is a hallmark of various diseases, including atherosclerosis, diabetes, rheumatoid arthritis, and cancer. In these conditions, macrophages often undergo metabolic reprogramming that sustains their pro-inflammatory state, contributing to disease progression.

In atherosclerosis, macrophages ingest oxidized low-density lipoproteins (oxLDL), transforming into foam cells. These foam cells exhibit impaired mitochondrial function and increased glycolytic activity, leading to the production of pro-inflammatory cytokines and ROS. The sustained inflammatory environment promotes plaque instability and increases the risk of cardiovascular events [24-26].

In diabetes, particularly type 2 diabetes, elevated glucose levels lead to increased glycolytic flux in macrophages. This metabolic shift enhances the production of inflammatory mediators and ROS, contributing to insulin resistance and pancreatic β-cell dysfunction. Additionally, the accumulation of advanced glycation end-products (AGEs) can further exacerbate macrophage activation and chronic inflammation [27].

Rheumatoid arthritis (RA) is characterized by persistent synovial inflammation. Macrophages in the synovial tissue exhibit increased glycolysis and FAO, processes that support their pro-inflammatory functions. The metabolic alterations in RA macrophages are associated with the production of inflammatory cytokines and matrix metalloproteinase, leading to joint destruction [28].

In cancer, tumor-associated macrophages (TAMs) are often reprogrammed to support tumor growth and metastasis. The tumor microenvironment, characterized by hypoxia and nutrient deprivation, induces metabolic changes in TAMs, promoting glycolysis and FAO. These metabolic adaptations enable TAMs to produce immunosuppressive cytokines and support tumor angiogenesis. Figure (2), illustrates the Macrophage Metabolic Reprogramming in Chronic Inflammation [29].

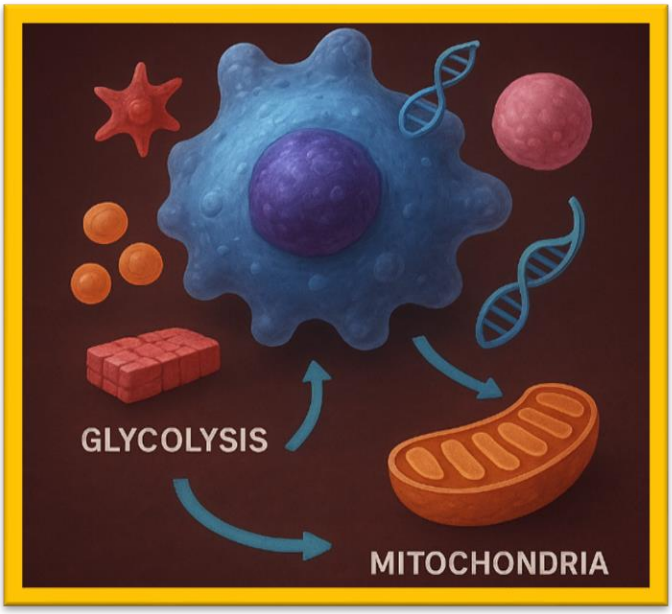

Figure 2. Macrophage Metabolic Reprogramming in Chronic Inflammation

Mechanisms Underlying Macrophage Metabolic Reprogramming

The metabolic reprogramming of macrophages is regulated by various intrinsic and extrinsic factors. Intrinsically, signaling pathways such as the mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and sirtuins play crucial roles in sensing cellular energy status and modulating metabolic pathways accordingly [30].

mTOR is a central regulator of cell metabolism and growth. In M1 macrophages, mTOR activation promotes glycolysis and the inflammatory response. Conversely, in M2 macrophages, mTOR inhibition favors OXPHOS and anti-inflammatory functions [31].

AMPK acts as an energy sensor, activating catabolic pathways to restore energy balance. In macrophages, AMPK activation enhances FAO and OXPHOS, promoting an anti-inflammatory phenotype. The activation of AMPK has been shown to suppress the production of pro-inflammatory cytokines and reduce tissue damage in chronic inflammatory diseases.

Sirtuins, particularly SIRT1, are NAD+-dependent deacetylases that regulate various metabolic processes. SIRT1 activation enhances mitochondrial function and promotes an anti-inflammatory response in macrophages. In chronic inflammatory conditions, the activity of SIRT1 is often reduced, leading to metabolic dysregulation and sustained inflammation.

Extrinsically, the tissue microenvironment plays a significant role in shaping macrophage metabolism. Factors such as oxygen levels, nutrient availability, and the presence of pathogens or damage-associated molecular patterns (DAMPs) influence the metabolic pathways utilized by macrophages. For instance, hypoxia in tissues leads to the stabilization of HIF-1α, promoting glycolysis and the M1 phenotype. In contrast, the presence of fatty acids and other metabolites can activate PPAR-γ and LXRs, driving the M2 phenotype.

Comparative Analysis with Existing Literature

Recent reviews have highlighted the critical role of macrophage metabolic reprogramming in chronic inflammation. For example, a study by Guo et al. (2021) discusses how the metabolic switch between M1 and M2 macrophages influences disease progression and recovery. They emphasize the importance of understanding these metabolic pathways to develop targeted therapies for chronic inflammatory diseases.

Similarly, a review by Ray et al. (2023) examines the diverse roles of macrophages in metabolic inflammation, focusing on conditions like insulin resistance and atherosclerosis. They note that metabolic reprogramming in macrophages contributes to the pathogenesis of these diseases and suggest that targeting metabolic pathways could offer therapeutic benefits.

Makassy et al. (2025) provide an in-depth analysis of the alterations in substrate uptake, storage, and oxidation in macrophages during inflammation. They highlight the complexity of macrophage metabolism and its impact on immune responses, underscoring the need for further research to unravel these mechanisms.

These studies collectively underscore the significance of macrophage metabolic reprogramming in chronic inflammation. They provide a comprehensive understanding of how metabolic pathways influence macrophage function and contribute to disease progression, aligning with the findings presented in this background.

Macrophage metabolic reprogramming is a fundamental process that dictates macrophage function and plays a pivotal role in the progression of chronic inflammatory diseases. Understanding the intricate relationship between metabolism and macrophage polarization offers new avenues for therapeutic intervention. By targeting specific metabolic pathways, it may be possible to modulate macrophage activity, thereby alleviating chronic inflammation and improving disease outcomes [32].

Mechanisms of Macrophage Metabolic Reprogramming

Metabolic Pathways in Macrophage Activation:

Macrophage activation represents a cornerstone of the innate immune response, shaping both protective immunity and the pathological mechanisms underlying chronic inflammatory diseases. Over the past decade, extensive research has elucidated the intricate relationship between macrophage metabolic pathways and their functional phenotypes, revealing that energy metabolism is not merely a supportive process but a primary regulator of immune responses. This paradigm shift has redefined our understanding of macrophage biology, highlighting the significance of metabolic reprogramming as a determinant of macrophage polarization, cytokine production, and overall immunological behavior.

The central finding from numerous studies is that macrophages adopt distinct metabolic programs depending on their activation state and the micro environmental cues they receive. Classically activated M1 macrophages, induced by stimuli such as lipopolysaccharide (LPS) and interferon-gamma (IFN-γ), exhibit a profound reliance on aerobic glycolysis. This metabolic adaptation allows for rapid ATP production, fulfilling the high energetic and biosynthetic demands required for the synthesis of pro-inflammatory cytokines, reactive oxygen species (ROS), and nitric oxide (NO) [33]. Moreover, the accumulation of specific metabolic intermediates such as succinate serves as a signaling mechanism, stabilizing hypoxia-inducible factor 1-alpha (HIF-1α) and enhancing the transcription of pro-inflammatory genes. The metabolic rewiring in M1 macrophages also involves a disruption of the tricarboxylic acid (TCA) cycle, leading to the accumulation of citrate, which supports fatty acid and prostaglandin synthesis, further amplifying inflammatory responses.

Conversely, alternatively activated M2 macrophages, stimulated by interleukin-4 (IL-4) and interleukin-13 (IL-13), rely predominantly on oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO). This metabolic profile is characterized by efficient ATP generation and enhanced mitochondrial respiration, supporting anti-inflammatory functions, tissue repair, and resolution of inflammation. In M2 macrophages, TCA cycle flux remains largely intact, providing biosynthetic intermediates for amino acid and nucleotide synthesis. Additionally, oxidative metabolism in M2 macrophages contributes to the production of anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), establishing a feedback loop that reinforces the anti-inflammatory phenotype [34].

The convergence of metabolism and immune signaling extends beyond these two canonical phenotypes. Recent research has revealed that macrophage metabolic states exist along a continuum rather than as discrete categories. Environmental factors such as hypoxia, nutrient availability, lipid overload, and pathogen-derived signals dynamically shape macrophage metabolism, creating a spectrum of functional states tailored to specific tissue contexts. For example, in tumor microenvironments, tumor-associated macrophages (TAMs) exhibit metabolic flexibility, simultaneously engaging glycolysis and oxidative pathways to support immunosuppressive functions, angiogenesis, and tumor progression. In metabolic diseases such as obesity and type 2 diabetes, adipose tissue macrophages display enhanced glycolysis and fatty acid accumulation, perpetuating chronic low-grade inflammation and insulin resistance. These observations underscore that metabolic programming is context-dependent and intimately linked to the tissue microenvironment, highlighting the need for nuanced therapeutic strategies that account for macrophage heterogeneity.

At the molecular level, the regulation of macrophage metabolism involves a complex interplay between signaling pathways and transcription factors. Key regulators such as the mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and sirtuins act as metabolic sensors that integrate intracellular energy status with external cues. mTOR signaling promotes glycolysis and anabolic processes in M1 macrophages, while AMPK activation supports FAO and OXPHOS in M2 macrophages [35].

Additionally, transcription factors including HIF-1α, peroxisome proliferator-activated receptor gamma (PPAR-γ), and liver X receptors (LXRs) modulate gene expression programs that coordinate metabolic activity with immune functions. Dysregulation of these signaling nodes often leads to pathological inflammation, highlighting their potential as therapeutic targets.

From a translational perspective, understanding metabolic pathways in macrophage activation has significant clinical implications. Targeted modulation of macrophage metabolism offers opportunities to treat a variety of chronic inflammatory and immune-mediated diseases. Pharmacological interventions that inhibit glycolysis in pro-inflammatory macrophages or enhance oxidative metabolism in anti-inflammatory macrophages have shown promise in preclinical models of atherosclerosis, rheumatoid arthritis, and metabolic syndrome [36].

Nutritional and lifestyle interventions, including caloric restriction, ketogenic diets, and omega-3 fatty acid supplementation, can similarly influence macrophage metabolism, shifting the balance toward anti-inflammatory states. Emerging approaches, such as nanoparticle-mediated delivery of metabolic modulators, provide the means to achieve tissue-specific targeting, minimizing systemic side effects and enhancing therapeutic efficacy.

Despite these advances, several challenges remain. Macrophage metabolism is highly plastic and context-dependent, and systemic modulation of metabolic pathways may inadvertently affect other immune or non-immune cells, leading to unintended consequences. Furthermore, inter-individual variability, influenced by genetic, epigenetic, and environmental factors, complicates the development of universally effective therapies. High-resolution techniques, including single-cell metabolomics, spatial transcriptomic, and metabolic flux analysis, are essential for dissecting the heterogeneity of macrophage metabolic states within tissues. Integration of these approaches with computational modeling and systems biology will provide a comprehensive understanding of the dynamic interplay between metabolism and immune function [37].

In conclusion, metabolic pathways are fundamental determinants of macrophage activation and function. The metabolic reprogramming of macrophages governs their polarization, cytokine production, and effector mechanisms, directly influencing the progression and resolution of inflammation. Insights into the molecular mechanisms that regulate these pathways have revealed new opportunities for therapeutic intervention in chronic inflammatory diseases. Future research must continue to elucidate the context-specific roles of metabolic pathways, exploring strategies to selectively modulate macrophage function without compromising host defense. By bridging the fields of immunology and metabolism, researchers can develop innovative approaches to restore immune homeostasis, mitigate chronic inflammation, and improve clinical outcomes. Understanding and manipulating macrophage metabolism represents not only a fundamental advance in immunology but also a transformative avenue for the development of next-generation therapeutics aimed at a wide spectrum of chronic diseases

Metabolic Intermediates as Signaling Molecules

Metabolic intermediates have emerged as pivotal regulators of macrophage function, bridging the gap between cellular metabolism and immune signaling. Beyond their classical roles as substrates in energy production and biosynthetic pathways, metabolites such as succinate, itaconate, citrate, α-ketoglutarate, and fumarate act as intrinsic signaling molecules that directly influence macrophage activation, polarization, and inflammatory responses. This dual functionality underscores the concept that metabolism is not merely a support system for cellular activity but a central determinant of immune cell behavior [38].

Succinate, for instance, accumulates in classically activated M1 macrophages and serves as a key signaling mediator by stabilizing hypoxia-inducible factor 1-alpha (HIF-1α), thereby enhancing the transcription of pro-inflammatory cytokines such as IL-1β. This metabolite exemplifies how TCA cycle intermediates can act as immunomodulatory signals, linking alterations in central carbon metabolism to inflammatory gene expression. Similarly, citrate exported from mitochondria contributes to the generation of Acetyl-CoA for histone acetylation and fatty acid synthesis, modulating both epigenetic and inflammatory programs in macrophages. These processes highlight the capacity of metabolites to integrate metabolic flux with functional outcomes.

Itaconate, derived from cis-aconitate via the enzyme immune-responsive gene 1 (IRG1), represents another critical signaling metabolite with potent anti-inflammatory properties. Itaconate inhibits succinate dehydrogenase (SDH), thereby modulating reactive oxygen species production and dampening NLRP3 inflammasome activation. Furthermore, itaconate activates the transcription factor NRF2, promoting antioxidant responses and supporting the resolution of inflammation. Such dual pro- and anti-inflammatory regulatory roles of metabolic intermediates reveal the fine-tuned balance that macrophages maintain through metabolic signaling.

Other metabolites, including α-ketoglutarate and fumarate, also exert significant regulatory effects. α-Ketoglutarate promotes the differentiation of anti-inflammatory M2 macrophages by influencing epigenetic marks and transcriptional programs, while fumarate accumulation can drive post-translational modifications that enhance inflammatory responses. These findings collectively demonstrate that metabolites are not passive participants but active determinants of macrophage phenotype and function.

Understanding the role of metabolic intermediates as signaling molecules has profound therapeutic implications. Targeting these pathways offers opportunities to modulate macrophage activation selectively, attenuate chronic inflammation, and restore tissue homeostasis. Pharmacological modulation of succinate, itaconate, or α-ketoglutarate levels can potentially shift macrophages toward resolving or anti-inflammatory phenotypes, thereby mitigating tissue damage in conditions such as atherosclerosis, diabetes, rheumatoid arthritis, and cancer. Moreover, integrating metabolic profiling with immunological studies allows for the identification of context-specific therapeutic targets and the development of precision interventions.

In conclusion, metabolic intermediates serve as critical signaling molecules that orchestrate macrophage function and inflammatory responses. Their roles extend beyond energy production to include epigenetic regulation, modulation of transcription factors, and direct influence on cytokine secretion. By elucidating these mechanisms, researchers can gain deeper insights into the interface between metabolism and immunity, ultimately guiding the development of innovative therapies aimed at controlling chronic inflammation and disease progression. Recognition of metabolites as integral signaling entities represents a transformative advancement in immunometabolism, reinforcing the centrality of metabolic regulation in shaping immune cell behavior. Figure (3) shows the Metabolic Intermediates as Signaling Molecules.

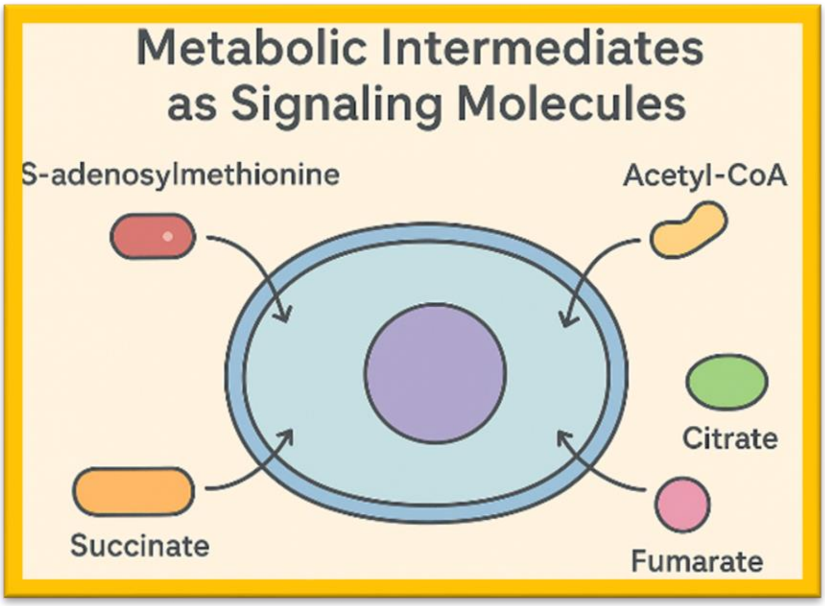

Figure 3. Metabolic Intermediates as Signaling Molecules

Metabolic Reprogramming and Chronic Inflammation

Metabolic reprogramming in macrophages is increasingly recognized as a central mechanism underlying the initiation, maintenance, and exacerbation of chronic inflammation. Chronic inflammatory diseases, including atherosclerosis, type 2 diabetes, rheumatoid arthritis, and certain neurodegenerative conditions, are characterized by persistent activation of macrophages in which metabolic shifts reinforce pro-inflammatory phenotypes. Unlike acute immune responses, where metabolic adaptations are transient and serve protective functions, sustained metabolic reprogramming in chronic inflammation drives pathological outcomes by perpetuating cytokine production, reactive oxygen species (ROS) generation, and tissue damage [39].

A fundamental insight from recent research is that metabolic reprogramming is not merely a byproduct of macrophage activation but an active determinant of inflammatory fate. Pro-inflammatory M1-like macrophages rely heavily on aerobic glycolysis, which enables rapid ATP generation and supplies biosynthetic intermediates required for the production of inflammatory mediators. This glycolytic program is reinforced by disruptions in the tricarboxylic acid (TCA) cycle, leading to the accumulation of signaling metabolites such as succinate, which further stabilize hypoxia-inducible factor 1-alpha (HIF-1α) and amplify pro-inflammatory gene transcription. In contrast, anti-inflammatory M2-like macrophages utilize oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO), metabolic pathways that support energy-efficient ATP production and promote the resolution of inflammation. Dysregulation of these pathways in chronic inflammatory contexts leads to an imbalance favoring sustained M1 polarization, thereby exacerbating tissue pathology.

Comparative analyses across disease models demonstrate that metabolic reprogramming serves as a common pathogenic mechanism. In atherosclerosis, foam cells with impaired mitochondrial respiration and enhanced glycolysis secrete pro-inflammatory cytokines that destabilize vascular plaques. In type 2 diabetes, hyperglycemia induces metabolic shifts that elevate glycolytic flux and ROS production in adipose tissue macrophages, reinforcing insulin resistance and systemic inflammation. Neurodegenerative diseases such as Alzheimer’s disease also reveal a link between metabolic dysfunction and chronic microglial activation, where impaired mitochondrial function and disrupted energy homeostasis contribute to sustained neuroinflammation and neuronal injury. These findings collectively illustrate that metabolic reprogramming is a conserved mechanism through which macrophages perpetuate chronic inflammatory states across diverse pathologies.

Therapeutically, targeting macrophage metabolism offers promising strategies for mitigating chronic inflammation. Modulation of glycolysis, enhancement of mitochondrial function, or pharmacological activation of energy-sensing pathways such as AMP-activated protein kinase (AMPK) can shift macrophages from pro-inflammatory to anti-inflammatory phenotypes. Nutrient-based interventions, including omega-3 fatty acids, caloric restriction, and ketone bodies, further highlight the potential for metabolic modulation to restore immune balance. Emerging techniques in single-cell metabolomics and spatial transcriptomics provide unprecedented resolution in mapping metabolic heterogeneity within macrophage populations, enabling precision targeting of pathological subpopulations.

In conclusion, macrophage metabolic reprogramming constitutes a pivotal mechanism linking cellular metabolism to chronic inflammation and disease progression. By defining the metabolic programs that govern macrophage polarization and effector function, researchers have uncovered both mechanistic insights and translational opportunities. Targeted interventions aimed at correcting metabolic imbalances hold substantial promise for reducing chronic inflammation, preventing tissue damage, and improving clinical outcomes across a spectrum of chronic diseases. Understanding and manipulating these metabolic pathways represents a critical frontier in immunometabolism, emphasizing the integral role of macrophage metabolism in shaping long-term inflammatory responses and guiding the development of next-generation therapeutics

Disease-Specific Roles of Macrophage Metabolism

Atherosclerosis: In atherosclerosis, macrophages engulf oxidized low-density lipoproteins (oxLDL), transforming into foam cells. These cells exhibit defective cholesterol efflux and metabolic stress that activate the NLRP3 inflammasome. Glycolytic enzymes like hexokinase 2 are upregulated, promoting IL-1β secretion. Inhibition of glycolysis or enhancement of mitochondrial oxidative capacity reduces plaque inflammation and stabilizes lesions.

Diabetes Mellitus

Hyperglycemia alters macrophage metabolism by enhancing glucose uptake and flux through the pentose phosphate pathway. This shift increases NADPH and ROS generation, sustaining chronic inflammation and endothelial damage. AMPK activation, by contrast, restores metabolic balance and improves insulin sensitivity by promoting FAO and anti-inflammatory cytokine release [40].

Cancer

Tumor-associated macrophages (TAMs) undergo metabolic adaptation to hypoxic and nutrient-deprived environments. These macrophages exhibit increased glycolysis and glutamine metabolism, supporting immunosuppression and tumor angiogenesis. Targeting metabolic enzymes such as IDO1 or PFKFB3 can reprogram TAMs toward a tumoricidal phenotype.

Neurodegenerative Diseases

In Alzheimer’s disease, microglia (the brain’s macrophages) display impaired mitochondrial function and reduced autophagy. These metabolic defects promote accumulation of β-amyloid and neuroinflammation. Enhancing mitochondrial biogenesis through PGC-1α activation restores microglial homeostasis and reduces neurodegeneration.

Therapeutic Implications and Future Directions

The therapeutic potential of targeting macrophage metabolic reprogramming represents a transformative frontier in the treatment of chronic inflammatory diseases. Macrophages, by virtue of their metabolic plasticity, serve as both mediators and modulators of inflammation. The identification of key metabolic pathways glycolysis, oxidative phosphorylation (OXPHOS), fatty acid oxidation (FAO), and amino acid metabolism as regulators of macrophage polarization has opened novel avenues for intervention. Unlike conventional anti-inflammatory therapies that broadly suppress immune responses, metabolic targeting offers the ability to selectively modulate macrophage function, shifting the balance from pro-inflammatory (M1-like) to anti-inflammatory or tissue-reparative (M2-like) phenotypes. This precision holds significant promise for reducing tissue damage while preserving host defense mechanisms.

Several strategies have emerged to exploit this metabolic plasticity. Pharmacological inhibition of glycolytic enzymes, such as hexokinase 2 or phosphofructokinase, can attenuate pro-inflammatory cytokine production in M1 macrophages. Conversely, activation of AMP-activated protein kinase (AMPK) or peroxisome proliferator-activated receptor gamma (PPAR-γ) promotes FAO and OXPHOS, favoring anti-inflammatory macrophage functions. Nutritional and metabolic interventions, including caloric restriction, ketogenic diets, and supplementation with omega-3 fatty acids, further demonstrate the capacity to modulate macrophage metabolism and systemic inflammatory responses. Emerging evidence also supports the use of nanoparticle-based delivery systems to target metabolic modulators directly to macrophage populations in diseased tissues, enhancing efficacy while minimizing off-target effects.

The integration of advanced technologies, such as single-cell metabolomics, spatial transcriptomics, and metabolic flux analysis, has provided unprecedented insights into the heterogeneity and plasticity of macrophage populations within tissues. These high-resolution approaches enable the identification of disease-specific metabolic signatures and the mapping of macrophage subpopulations that contribute disproportionately to chronic inflammation. Such precision profiling facilitates the development of context-specific therapeutic strategies, allowing interventions to be tailored to the metabolic and functional state of macrophages in a given disease environment.

Despite these advances, several challenges remain. The systemic modulation of metabolic pathways carries the risk of unintended effects on other immune or non-immune cells. Additionally, the dynamic and context-dependent nature of macrophage metabolism necessitates careful consideration of disease stage, tissue microenvironment, and patient-specific factors when designing interventions. Longitudinal studies and clinical trials are essential to establish the safety, efficacy, and optimal timing of metabolic-based therapies in chronic inflammatory conditions.

In conclusion, therapeutic targeting of macrophage metabolic reprogramming represents a paradigm shift in immunotherapy. By leveraging the intrinsic link between metabolism and immune function, it is possible to modulate macrophage polarization, resolve chronic inflammation, and mitigate disease progression. Future research should focus on elucidating the precise molecular mechanisms governing metabolic control in macrophages, developing selective modulators, and translating these findings into clinical practice. The convergence of immunology, metabolism, and translational medicine holds the potential to yield innovative, precise, and effective therapies for a broad spectrum of chronic inflammatory diseases, ultimately improving patient outcomes and advancing the field of immunometabolism [24].

Discussion and Analysis of Results

Macrophage metabolic reprogramming has emerged as a pivotal mechanism in regulating chronic inflammation and disease progression, attracting significant attention in recent immunological research. Numerous studies indicate that macrophages can modulate inflammatory phases and disease trajectories by dynamically adjusting their metabolic pathways.

Impact of Metabolic Pathways on Macrophage Polarization

Metabolic pathways directly influence macrophage polarization and functional phenotypes. Under inflammatory conditions, macrophages predominantly rely on aerobic glycolysis, enabling rapid energy production and the accumulation of signaling intermediates such as succinate. Succinate stabilizes hypoxia-inducible factor 1-alpha (HIF-1α), enhancing the transcription of pro-inflammatory cytokines such as IL-1β (Tannahill et al., 2013; PMC8056050). This mechanistic insight highlights how central carbon metabolism is intricately linked to immune gene expression and inflammatory outputs [38].

Metabolic Reprogramming in Chronic Disease Contexts

Chronic diseases, including atherosclerosis, type 2 diabetes, and inflammatory bowel disease (IBD), demonstrate disease-specific patterns of macrophage metabolic reprogramming. In atherosclerosis, foam cells with disrupted mitochondrial function and elevated glycolysis produce pro-inflammatory mediators that exacerbate plaque formation and instability. In type 2 diabetes, hyperglycemia triggers metabolic shifts in adipose tissue macrophages, increasing glycolytic flux and reactive oxygen species (ROS) production, thereby perpetuating insulin resistance and systemic inflammation (Lumeng et al., 2007). Similarly, in IBD, metabolically reprogrammed macrophages activate pathways such as NLRP3 inflammasome signaling, increasing cytokine secretion and driving persistent intestinal inflammation (Jha et al., 2015; Dovepress).

Role of Metabolic Intermediates in Immune Regulation

Intermediate metabolites, including succinate, itaconate, and α-ketoglutarate, play crucial roles in signaling pathways that determine macrophage function. For instance, itaconate, produced via the IRG1 enzyme, inhibits succinate dehydrogenase (SDH) and reduces ROS production, thereby suppressing NLRP3 inflammasome activation. It also activates NRF2-mediated antioxidant responses, contributing to the resolution of inflammation (Lampropoulou et al., 2016). Similarly, α-ketoglutarate supports the differentiation of anti-inflammatory M2 macrophages by modulating epigenetic and transcriptional programs, emphasizing the bidirectional regulation between metabolism and macrophage polarization [39].

Challenges and Opportunities

Despite substantial progress, challenges remain in translating these findings into clinical interventions. The complexity and tissue-specific variability of macrophage metabolic pathways can result in heterogeneous responses, complicating therapeutic strategies. Moreover, precise diagnostic tools are needed to accurately profile macrophage metabolic states in vivo. Nonetheless, these challenges present opportunities for the development of targeted interventions. Small molecules, metabolic modulators, and nanoparticle-based delivery systems may selectively reprogram macrophage metabolism, shifting them toward anti-inflammatory or tissue-reparative phenotypes, offering novel strategies for controlling chronic inflammation [40].

Conclusion

Macrophage metabolic reprogramming serves as a central regulator of chronic inflammation and disease progression. Alterations in glycolysis, oxidative metabolism, and lipid handling drive macrophage polarization and shape the inflammatory microenvironment. Understanding these mechanisms bridges the gap between metabolism and immunity, providing a conceptual framework for novel therapeutic interventions. Future research should focus on selectively targeting metabolic checkpoints to restore immune balance without compromising host defense.

In conclusion, macrophage metabolic reprogramming serves as a central mechanism governing chronic inflammation and disease progression. Insights into metabolic pathways, intermediate metabolites, and context-specific reprogramming provide critical mechanistic understanding and highlight potential therapeutic targets. By leveraging these findings, researchers can develop innovative, precision-based approaches to modulate macrophage activity, reduce chronic inflammation, and mitigate disease pathology. Continued investigation into the molecular and metabolic underpinnings of macrophage function will be essential for translating these insights into effective therapies for a broad spectrum of chronic inflammatory conditions

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Authors' Contributions

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