Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

The Role of Pattern Recognition Receptors in Epigenetic and Metabolic Reprogramming: Insights into Trained Immunity

Yanjie Li[1,2], Mingzhu Chen[1,2], Junxiong Li[1,2], Jiangtian Hu[1,2]

[1]Department of Orthodontics, Kunming Medical University School and Hospital of Stomatology, Kunming, 650106, People's Republic of China; [2]Yunnan Key Laboratory of Stomatology, Kunming, 650106, People's Republic of China

Correspondence: Jiangtian Hu, Email hujiangtian@kmmu.edu.cn

Abstract: Pattern recognition receptors (PRRs) function as pivotal components of the innate immune system by orchestrating trained immunity through dynamic epigenetic and metabolic reprogramming. Recent discoveries demonstrate that PRRs not only detect pathogens but also actively regulate immune cell metabolism and transcriptional landscapes, thereby potentiating the speed and magnitude of defensive responses upon secondary challenges. These functional adaptations are coordinated through evolutionarily conserved signaling cascades that establish persistent immunological modifications at cellular and systemic levels. Nevertheless, despite substantial advances in characterizing PRR-driven immune activation, the molecular mechanisms governing their role in innate immune memory formation remain incompletely elucidated. This review systematically explores emerging paradigms of PRR-mediated epigenetic remodeling and metabolic rewiring, with particular emphasis on their mechanistic integration into trained immunity. We critically assess current evidence, identify unresolved questions regarding signal transduction specificity and memory maintenance, and propose novel methodological approaches to decipher the multilayered regulatory networks of innate immune adaptation. By elucidating these processes, our analysis establishes a conceptual framework for developing immunomodulatory therapies and leveraging trained immunity in precision medicine applications.

Keywords: pattern recognition receptors, epigenetic, metabolic reprogramming, trained immunity, immunocyte

Introduction

Trained immunity (TI) is an evolutionarily conserved mechanism of innate immune memory that enhances nonspecific host defense through epigenomic and metabolic reprogramming. Unlike the antigen-specific memory conferred by adaptive immunity via T and B lymphocytes, TI predominantly engages myeloid lineage cells, including monocytes and macrophages. This functional rewiring is initiated through activation of germline-encoded PRRs, particularly Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), which recognize conserved pathogen-associated molecular patterns (PAMPs). PRR signaling triggers chromatin remodeling events characterized by histone modifications such as H3K4 trimethylation (H3K4me3), coupled with metabolic shifts toward aerobic glycolysis. These coordinated changes establish a transcriptionally permissive state for rapid cytokine gene activation, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). While adaptive immune memory provides lifelong protection, TI generally exhibits a shorter duration spanning weeks to months. Notably, dietary metabolites like β-glucans modulate the magnitude and persistence of TI by targeting epigenetic modifiers within transcriptional regulatory complexes. Thus, PRRs function as biochemical integrators that convert microbial encounters into sustained immune reprogramming. This paradigm shift in innate immune plasticity not only challenges traditional immunological frameworks but also offers novel therapeutic strategies for infectious diseases, cancer immunotherapy, and inflammation-related pathologies.[1,2]

Received: 19 December 2024
Accepted: 22 May 2025
Published: 13 June 2025

As central architects of immune memory, PRRs detect both PAMPs and damage-associated molecular patterns (DAMPs) to execute dual functions: triggering immediate host defense mechanisms[3,4] and coordinating sustained epigenetic-metabolic reprogramming for innate immune memory.[5–7] The activation of PRRs induces two mutually reinforcing processes—dynamic metabolic rewiring and stable epigenetic modifications—that synergistically enhance immune cell responsiveness to secondary challenges.[8,9] These molecular adaptations amplify antimicrobial effector functions while promoting cytokine production, creating metabolic-epigenetic imprints essential for TI establishment. Experimental models demonstrate that PRR recognition of bacterial components establishes persistent antimicrobial memory in myeloid cells, conferring robust protection against reinfection.[10–12] Such insights hold transformative potential for designing next-generation vaccines and immunotherapies.[13]

Critical knowledge gaps persist in deciphering PRR-mediated training mechanisms. Existing studies predominantly focus on PRR functions in pathogen detection and acute inflammatory signaling, with limited investigation into their roles in maintaining and regulating immune adaptation. Furthermore, the tissue-specific expression profiles and functional diversification of PRR subsets remain poorly characterized, particularly in pathological contexts such as chronic inflammation, autoimmunity, and tumor microenvironments.

Classification and Function of Pattern Recognition Receptors

Toll-Like Receptors (TLRs)

TLRs, recognized as the prototypical and evolutionarily conserved family of transmembrane PRRs, are classified into 13 functional subtypes in mice (TLR1-TLR13) and 10 in humans (TLR1-TLR10), based on their ligand specificity and subcellular localization. Cell membrane-resident TLRs—specifically TLR1, TLR2, TLR4, TLR5, and TLR6—primarily detect microbial membrane components such as bacterial lipoproteins (TLR1/2/6), lipopolysaccharide (LPS, sensed by TLR4), and flagellin (TLR5). In contrast, intracellular TLRs localized to endosomal compartments (TLR3, TLR7, TLR8, and TLR9) recognize viral nucleic acids including double-stranded RNA (TLR3), single-stranded RNA (TLR7/8), and unmethylated CpG DNA (TLR9).[14–16] Upon LPS binding, TLR4 undergoes dimerization and recruits the adaptor protein Myeloid Differentiation Primary Response 88 (MyD88) via Toll/Interleukin-1 Receptor (TIR) domain interactions, initiating a multi-step signaling cascade. MyD88 mediates the assembly of Interleukin-1 Receptor-Associated Kinase 4 (IRAK4), which subsequently phosphorylates and activates Interleukin-1 Receptor-Associated Kinase 1 (IRAK1). This kinase activation leads to nuclear translocation of Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB). These coordinated events drive the transcriptional upregulation of pro-inflammatory cytokines such as TNF-α and IL-6, along with chemokines critical for immune cell recruitment.[17,18]

Expanding beyond microbial defense, emerging evidence reveals context-dependent roles of TLRs in tumor immunobiology. TLR agonists demonstrate dual functionality in oncological settings: they potentiate γδ T cell-mediated antitumor activity either directly or via dendritic cell activation, and synergize with tumor-associated antigens to enhance cytotoxic T lymphocyte (CTL) responses. Preclinical studies illustrate this therapeutic potential, as combined administration of TLR9 agonist CpG oligodeoxynucleotides (CpG ODN) with rlipo-E7m effectively amplifies CTL activity and achieves regression of established tumors.[19–21]

Nucleotide-Binding Oligomerization Domain-Like Receptors (NLRs)

NLRs are critical cytosolic PRRs orchestrating innate immune responses and inflammatory regulation. The NLR family is structurally classified into five subfamilies: (1) NLRA (characterized by an acidic transactivation domain, exemplified by class II transactivator, CIITA), (2) NLRB (bearing baculovirus inhibitor of apoptosis protein repeat, BIR, domains, as observed in neuronal apoptosis inhibitory protein, NAIP), (3) NLRC (containing caspase activation and recruitment domains, CARD, including nucleotide-binding oligomerization domain-containing proteins 1 and 2, NOD1 and NOD2, that activate NF-κB, and Mitogen-Activated Protein Kinase, MAPK, pathways through receptor-interacting serine/threonine-protein kinase 2, RIPK2, and transforming growth factor beta-activated kinase 1, TAK1, signaling complexes), (4) NLRP (defined by pyrin domain-containing

members such as NLRP1 and NLRP3), and (5) NLRX (localized to mitochondrial membranes).[22,23] Functioning as intracellular surveillance systems, NLRs detect PAMPs from invading microbes and DAMPs released by stressed or necrotic cells, serving as central hubs for cytosolic danger signal integration.[24–27] Mechanistically, specific NLR subfamilies – particularly NLRP3 – nucleate inflammasome complexes that catalyze caspase-1-dependent proteolytic maturation of interleukin-1 beta (IL-1β) and interleukin-18 (IL-18), key pro-inflammatory cytokines essential for driving leukocyte infiltration and tissue remodeling during microbial challenges.[28–30] Beyond antimicrobial defense, NLRs maintain tissue homeostasis through strict governance of inflammatory responses. Pathological NLR activation disrupts this equilibrium, as demonstrated by inflammasome hyperactivity in autoimmune disorders including rheumatoid arthritis and inflammatory bowel disease, where IL-1β/IL-18 overproduction directly correlates with disease progression.[31–33] Emerging evidence implicates NLRP3 inflammasome dysregulation in chronic disease pathogenesis. In cardiovascular pathologies, persistent NLRP3 activation induces endothelial dysfunction and plaque instability, while in neurodegenerative conditions such as Alzheimer's disease, it potentiates neuroinflammatory cascades and amyloid-beta deposition.[34,35] These mechanistic insights establish NLR-mediated signaling pathways as promising therapeutic targets for chronic inflammatory diseases, either through direct inflammasome inhibition or downstream cytokine neutralization strategies.

C-Type Lectin Receptors (CLRs)

CLRs, as specialized PRRs, utilize conserved carbohydrate-recognition domains (CRDs) to detect pathogenic glycans (microbial-associated molecular patterns) and host damage signals. These receptors exist in membrane-bound (including CLEC7A and CLEC4E) and soluble forms (mannose-binding lectin), performing dual surveillance of exogenous microbial components (fungal β-glucans, mycobacterial glycolipids, viral glycoproteins) and endogenous glycocalyx integrity. Functionally, CLRs bridge innate and adaptive immunity through two distinct mechanisms: (1) Signal transduction via Syk-coupled CLRs: Specific members such as CLEC7A activate NF-κB/MAPK/IRF-mediated proinflammatory and antiviral pathways through β-glucan-induced signal transduction. This process initiates SYK kinase recruitment, followed by assembly of the caspase recruitment domain-containing protein 9 (CARD9)/B-cell lymphoma 10 (BCL10)/mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) ternary complex, ultimately driving TGF-β-activated kinase 1 (TAK1)-dependent downstream cascades. (2) Antigen presentation via endocytic CLRs: Receptors like DEC-205 facilitate dendritic cell-dependent antigen processing and presentation, thereby priming T-cell adaptive responses.[36,37]

Crucial for antifungal immunity, CLRs mediate recognition of clinically significant pathogens including Candida albicans and Aspergillus species through binding of surface carbohydrates, subsequently activating macrophages and dendritic cells to initiate pathogen clearance.[38–40] This interaction induces proinflammatory cytokine/chemokine production essential for leukocyte recruitment and coordinates dendritic cell maturation, thereby establishing innate-to-adaptive immune crosstalk.[41,42]

Emerging evidence expands CLR functionality in tumor immunology. Acting as multimodal regulators, CLRs modulate the tumor microenvironment by recognizing tumor-associated glycosylation patterns (mannose structures, Lewis antigens, GalNAc). These receptors exhibit dualistic roles in carcinogenesis: (a) tumor-suppressive through antigen-presenting cell-mediated immune activation, and (b) tumor-promoting via metastatic facilitation of malignant cells.[43,44] Furthermore, CLRs mediate endocytic antigen processing and directly regulate T-cell activation thresholds. Therapeutic strategies targeting CLRs are under investigation, including Clec4e/Dectin-1 blocking antibodies that attenuate neutrophil-mediated tumor cytotoxicity in murine models.[45,46]

RIG-I-Like Receptors (RLRs)

The retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), constituting a specialized subclass of cytosolic RNA-sensing PRRs, detect viral nucleic acids via conserved helicase and C-terminal regulatory domains. This receptor family comprises three structurally defined members: RIG-I (specific for short 5′-triphosphate RNA/dsRNA), MDA5 (selective for long dsRNA), and the regulatory co-factor LGP2, collectively executing viral

RNA surveillance through discrimination of pathogen signatures (eg, unshielded 5′-triphosphates) from host RNA degradation products.[47,48]

Mechanistically, RLR activation requires CARD domain-mediated oligomerization with the mitochondrial antiviral-signaling protein (MAVS). Recent structural insights demonstrate that the CARD:CARD interface between RLRs (specifically RIG-I and MDA5) and MAVS adopts a helical filamentous architecture, which serves as a supramolecular signaling platform (MAVS signalosome) by nucleating prion-like aggregates. This receptor-proximal interaction topology (RLR CARD helices engaging MAVS CARD surface grooves) enables tightly regulated signal amplification, where dynamic ubiquitination switches (TRIM25-mediated K63-ubiquitin chain deposition on RIG-I CARDs versus CYLD-mediated deubiquitination) and competitive inhibition (eg, NLRX1 C-terminal domain sterically blocking MAVS CARD accessibility) synergistically control antiviral response thresholds.[49,50] Activation of the MAVS signalosome recruits the TAK1 kinase complex, which bridges RLR-induced mitochondrial signaling to downstream NF-κB and MAPK pathways[48,51] (Figure 1).

Epigenetic Regulatory Mechanisms

DNA Methylation

DNA methylation, a fundamental epigenetic modification, involves the enzymatic transfer of methyl groups (-CH_3) to cytosine residues within cytosine-phosphate-guanine (CpG) islands—genomic regions enriched in cytosine-guanine

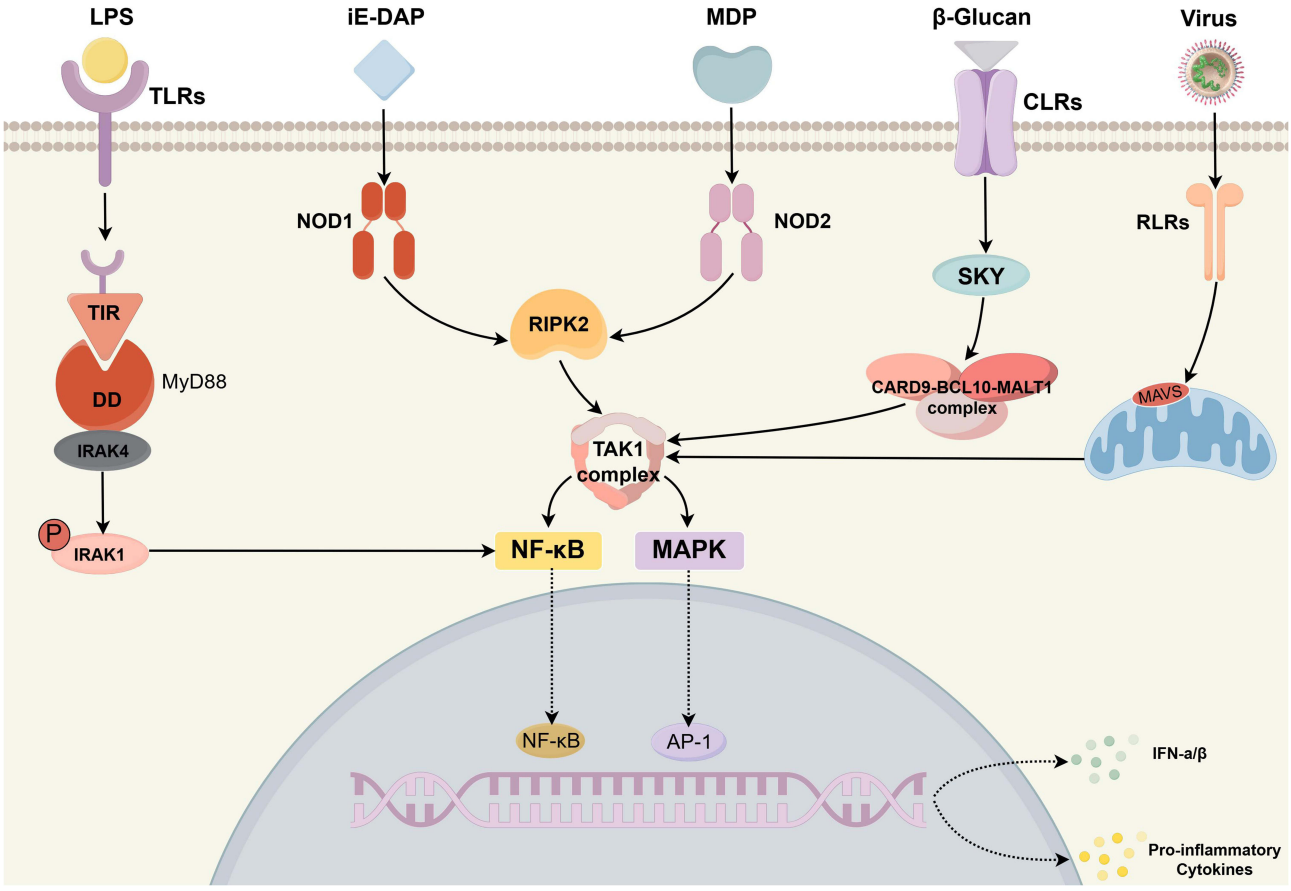

Figure 1 PRRs regulate intracellular immune responses and trigger the release of pro-inflammatory cytokines and interferons. LPS activates TLR4 to recruit TIRAP and MyD88, forming a complex that phosphorylates IRAK4 and IRAK1, leading to activation of the NF-κB pathway for pro-inflammatory gene transcription. NOD1/2 recognize bacterial ligands (iE-DAP/MDP) and engage RIP2, which orchestrates TAK1 complex-dependent activation of NF-κB and MAPK pathways to amplify cytokine responses. CLRs detect β-glucans and trigger assembly of the CARD9/BCL10/MALT1 signaling complex, which activates TAK1-mediated NF-κB and MAPK pathways. RLRs bind viral RNA to induce MAVS aggregation, activating TAK1 for NF-κB/MAPK signaling and recruiting TBK1/IKKε kinases to phosphorylate IRF3/IRF7, thereby promoting interferon synthesis. (Created with Figdraw).

dinucleotide repeats. This covalent modification induces transcriptional silencing through dual mechanisms: chromatin condensation and steric hindrance of transcription factor binding.[52,53] Unlike transient transcriptional fluctuations, persistent methylation anomalies demonstrate causal involvement in diverse pathologies ranging from neoplastic progression (including breast and cervical carcinomas) to cardiovascular diseases and metabolic dysregulation.[54–56]

Pathological epigenetic reprogramming predominantly operates through two molecular axes: (1) promoter hypermethylation-mediated inactivation of tumor suppressor genes (exemplified by *MRVI1* and *NTRK3* silencing during cervical carcinogenesis), and (2) DNA methyltransferase (DNMT)-dependent dysregulation of non-coding RNAs. The latter mechanism is typified by hypermethylation-induced suppression of tumor-suppressive microRNAs (miR-29c, miR-200c, and miR-200a) that confers chemoresistance in breast adenocarcinoma.[57,58] Beyond transcriptional control, methylation dynamics orchestrate cellular differentiation, developmental morphogenesis, and environmental adaptation through spatiotemporal methylome remodeling.[59–61] Advanced methylome profiling technologies—bisulfite sequencing, single-cell methylomics, and nanopore-based detection—now enable high-resolution mapping of disease-associated epimutations. These methodologies systematically identify functionally relevant methylation signatures at loci such as *CDKN2A/p16* (cell cycle regulation) and *MLH1* (DNA repair).[62,63] Such epigenomic insights facilitate two therapeutic strategies: pharmacological DNMT inhibition (decitabine and azacitidine) and precision epigenetic editing using CRISPR-dCas9 systems targeting aberrantly methylated promoters.

Histone Modification

Histone modification serves as a crucial epigenetic regulatory mechanism through chemical modifications such as methylation, acetylation, and phosphorylation, which influence chromatin structure and regulate gene accessibility and expression.[64,65] Distinct histone modifications exert specific regulatory effects. For example, histone H3 acetylation generally activates gene transcription, whereas H3 methylation predominantly represses transcriptional activity. As a key metabolic byproduct, lactate enhances histone H3K27 acetylation, thereby activating nuclear receptor subfamily 4 group A member 1 (*Nr4a1*) and suppressing pro-inflammatory pathways in macrophages. This lactate-induced acetylation mediates sustained "trained immunosuppression" by establishing long-term chromatin remodeling. Furthermore, nucleosomes physically block DNMTs from accessing DNA, thereby limiting DNMT-mediated transcriptional repression.[66,67]

Dynamically regulated histone modifications coordinate essential biological processes, including cell cycle progression and DNA damage repair, through chromatin state transitions.[68,69] These modifications precisely govern cellular functions such as proliferation, differentiation, and apoptosis. In cancer biology, aberrant histone modification landscapes drive tumorigenesis by silencing tumor suppressor genes and activating oncogenic pathways.[70,71] Consequently, therapies targeting these dysregulated mechanisms—notably histone deacetylase (HDAC) inhibitors—are emerging as effective anticancer strategies through epigenetic reprogramming and synergistic interactions with immunotherapy.[72]

Role of Non-Coding RNAs

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), play crucial roles in epigenetic regulation through diverse mechanisms such as direct mRNA interactions and transcription factor modulation.[73–75] Specific subtypes exert distinct regulatory functions: miRNAs primarily post-transcriptionally regulate gene expression through mRNA degradation or translational inhibition, profoundly influencing immunometabolic reprogramming processes including glycolysis and oxidative phosphorylation.[76–78] Conversely, lncRNAs coordinate epigenetic regulation through chromatin remodeling mechanisms by altering histone modification patterns and DNA methylation status, thereby directly controlling immune cell metabolism and trained immunity programs. For example, lncRNA-SNHG29 orchestrates genome-wide binding of EP300 (a histone acetyltransferase critical for metabolic reprogramming) to drive glycolytic activation in myeloid cells during innate immune responses, while lncRNA-GTL2 mediates DNA methylation-

dependent silencing of fatty acid oxidation genes in macrophages, illustrating the metabolic-epigenetic crosstalk in trained immunity.[79,80]

Notably, ncRNA dysregulation contributes significantly to tumorigenesis and cancer progression, frequently intersecting with immune cell metabolic pathways such as the Warburg effect.[81,82] These molecules demonstrate promising potential as diagnostic biomarkers due to their tissue-specific expression profiles, with emerging applications in cancer screening and prognostic assessment.[83,84] With increasing mechanistic understanding, ncRNA-targeted therapeutic strategies are under active exploration, particularly approaches modulating lncRNAs to normalize dysregulated immunometabolic pathways for precise disease intervention.[85–87]

PRRs Mediate Epigenetic Reprogramming of Immune Cells

PRR activation triggers profound chromatin reorganization and transcriptional remodeling in immune cells, establishing a primed state that enhances responsiveness to secondary challenges through amplified immune reactions. Mechanistically, PRR-mediated signaling orchestrates multi-layered epigenetic regulation via transcription factor modulation and chromatin modifications, including histone acetylation, methylation, and nucleosome repositioning.[88,89] The evolutionarily conserved TIR domain present in TLRs and related PRRs functions as a molecular scaffold for downstream adaptor recruitment (eg, MyD88, TRIF), initiating signal transduction. During LPS stimulation, TLR4 TIR domain acetylation facilitates oligomerization-enhanced adaptor binding, dramatically amplifying NF-κB signaling through IRAK4 activation and accelerated Inhibitor of Nuclear Factor kappa-B alpha (IκBα) degradation, reinforcing M1 macrophage polarization.[90]

TLR activation by LPS induces not only pro-inflammatory mediators but also persistent epigenetic signatures. IL-4-polarized macrophages subjected to LPS develop epigenetically encoded hyper-inflammatory programs, with sustained H3K27ac-driven transcriptional memory exacerbating pulmonary inflammation upon TLR rechallenge.[91] This TIR signaling-epigenetic crosstalk mechanistically links innate immune activation to metabolic-epigenetic memory. Primary inflammatory stimuli imprint microglial immune memory via H3K27ac, while pharmacological inhibition of this mark prevents secondary inflammatory amplification.[92] Tet methylcytosine dioxygenase 2 (TET2) exerts epigenetic control in atherogenesis, where TET2 deficiency enables cholesterol-loaded macrophages to activate NLRP3 via c-Jun N-terminal kinase 1(JNK1) signaling and BRCA1-Associated Protein 1 (BRCC3)-mediated deubiquitination.[93]

Recent studies demonstrate that PRR activation by microbial components can synergize with exogenous therapeutic interventions. For example, β-glucan-induced Dectin-1 signaling primes H3K27 acetylation at glycolytic gene loci,[94] a process that may amplify the metabolic effects of vitamin D adjuvants, which are known to enhance TLR2-mediated H3K4me3 deposition.[95,96] In oncological contexts, TLR3-activated IRF3 directly remodels antiviral response elements through interactions with oncolytic virus-derived RNA,[97] while CpG/TLR9 agonists have demonstrated clinical efficacy in eradicating cancer stem cells when combined with epigenetic checkpoint inhibitors.[98,99] These findings position PRR signaling as a highly tunable epigenetic scaffold for developing combination immunotherapies.

Metabolic Reprogramming

Metabolic reprogramming refers to the adaptive rewiring of cellular metabolic pathways to meet biosynthetic and bioenergetic demands under specific environmental or pathological conditions. This phenomenon has been systemically characterized across oncology, immunology, and metabolic disorders.[100–102] Through coordinated regulation of nutrient utilization and energy flux, cells dynamically reconfigure metabolic networks to sustain proliferation, survival, and effector functions. A hallmark example is the "Warburg effect" in malignancies, where tumor cells preferentially upregulate aerobic glycolysis despite functional mitochondria, concurrently suppressing oxidative phosphorylation to fuel anabolic growth and metastatic dissemination.[103–105]

In immunometabolic contexts, immune-responsive gene 1 (IRG1)-derived itaconic acid, synthesized by macrophages under pro-inflammatory stimuli (eg, LPS or IFN-γ), modulates T cell plasticity through dual mechanisms: (1) direct suppression of glycolysis and (2) epigenetic regulation, collectively ameliorating autoimmune pathologies. Furthermore,

IgG FcγR-mediated macrophage metabolic reprogramming, marked by mTOR- and HIF-1α-driven glycolytic upregulation, has emerged as a targetable axis in lupus nephritis. Within breast cancer microenvironments, hypoxia and nutrient competition drive tumor-associated macrophages (TAMs) to impede CD8+ T cell function via collagen accumulation and lactate-mediated metabolic interference (eg, disruption of oxidative phosphorylation), illustrating how spatial metabolic coupling dictates immune evasion.[106–108] These adaptive mechanisms not only underpin disease progression and immune dysregulation but also reveal novel therapeutic vulnerabilities. Key targets include the IRG1-itaconic acid signaling axis, rate-limiting glycolytic enzymes (eg, hexokinase 2, HK2), and lactate transport systems, offering multimodal intervention strategies across pathological states.

The Role of PRR in Metabolic Reprogramming

The activation of PRRs serves dual biological roles: modulating immune cell functions and orchestrating context-dependent metabolic reprogramming.[109,110] For instance, the TLR4 agonist LPS and other TLR ligands rapidly enhance the enzymatic activity of class IIa histone deacetylases (HDAC4, HDAC5, HDAC7, and HDAC9). This activity suppresses glycolysis and amplifies inflammatory responses by deacetylating key glycolytic enzymes such as 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3).[111] Additionally, TLR4 activation may inhibit AMP-activated protein kinase (AMPK) function by altering intracellular metabolic states. Given AMPK's anti-inflammatory role in suppressing pro-inflammatory mediators like NF-κB, this inhibition helps mitigate inflammation triggered by TLR signaling.[112] TLR signaling also modulates oxidative phosphorylation (OXPHOS) through the Phosphoinositide 3-kinase (PI3K)- Protein kinase B (AKT) and Janus kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) pathways, which are mechanistically linked to reactive oxygen species (ROS) generation. Such regulation augments OXPHOS and ROS production, ultimately enhancing antitumor immunity.[113] Beyond TLRs, other PRRs—including CLRs and RLRs—regulate immune cell metabolism via distinct mechanisms involving OXPHOS, amino acid metabolism, and mitochondrial dynamics. These findings underscore PRR-driven metabolic reprogramming as a source of therapeutic potential.[114] Targeting specific pathways, such as glycolysis, OXPHOS, or amino acid metabolism, could enable precise immunomodulation, exemplified by small-molecule inhibitors of HDACs or AMPK modulators, offering novel avenues for therapeutic intervention.[115,116]

Association of Metabolic Pathways with the Immune Response

Metabolic pathways are intricately intertwined with immune responses, as immune cells undergo metabolic reprogramming upon activation to sustain functional demands. This reprogramming not only fulfills the bioenergetic requirements of immune cells but also critically governs cytokine production and secretion by modulating signaling cascades, thereby enabling effective immune effector functions.[117–119] For example, macrophage phenotypic transitions are profoundly shaped by metabolic adaptation. Lactate enhances Pyruvate Kinase M2 (PKM2) lactylation, which inhibits its structural shift from tetrameric to dimeric states. This increases pyruvate kinase enzymatic activity while reducing PKM2 nuclear translocation, thereby driving pro-inflammatory macrophages toward a reparative phenotype.[120] Similarly, CH25H (cholesterol-25-hydroxylase)-mediated accumulation of 25-hydroxycholesterol (25HC) activates AMPKα and reprograms macrophage metabolism, which augments STAT6 activity to induce the immunosuppressive factor ARG1 (arginase 1).[121] In tolerogenic dendritic cells, Mammalian Target of Rapamycin (mTOR):AMPK phosphorylation balance shifts and increased OXPHOS, glycolysis, and fatty acid oxidation collectively establish an immunosuppressive phenotype characterized by PD-L1 and IL-10 upregulation to suppress T cell activation.[122]

The tumor microenvironment (TME) exemplifies the bidirectional crosstalk between metabolism and immune function. Tumor cells subvert immune surveillance by reshaping metabolic landscapes through mechanisms such as lactate accumulation and nutrient depletion, which directly impair immune cell efficacy.[123–125] Such metabolic rewiring constitutes a pivotal axis of tumor immune evasion and a persistent barrier to successful immunotherapy.[126,127] Therapeutic targeting of immune cell metabolism has emerged as a promising strategy. For instance, tumor-infiltrating T cells (TILs) are metabolically compromised in the TME due to metabolites like fatty acids that chronically activate acetyl-CoA carboxylase (ACC). ACC hyperactivity disrupts mitochondrial

energy synthesis required for antitumor activity. Pharmacological ACC inhibition reverses these defects, restores TIL functionality, and enhances tumor control.[128,129] Similarly, TAMs exhibit metabolic heterogeneity, with elevated purine metabolism being a hallmark of their pro-tumorigenic phenotype, positioning this pathway as a therapeutic vulnerability.[130]

Dietary factors further modulate TI plasticity. Short-chain fatty acids (SCFAs) from dietary fiber fermentation enhance β-glucan-induced TI by stabilizing HIF-1α-dependent histone acetylation in monocytes.[131] Conversely, high-fat diets suppress TI by disrupting TLR4-driven enhancer-promoter looping via PPARγ activation.[132] These insights collectively underscore TI as a dynamic interface between environmental cues and immune memory, where PRRs act as epigenetic sensors to transduce nutrient signals into functional immune adaptations.

Effects of PRRs on Trained Immunity

Primary Infection and Activation of Immune Cells

The initial infection represents a pivotal phase in the establishment of TI. During this stage, pathogens breach host barriers via the skin or mucosal surfaces, initiating a cascade of immune reactions. Macrophages and dendritic cells detect these pathogens through PRRs, triggering their activation.[133–135] Beyond immediate pathogen clearance through phagocytosis and neutralization, these cells amplify immune responses by recruiting additional effectors via cytokine secretion.[136] A hallmark of TI is the persistent metabolic and epigenetic remodeling of immune cells post-infection, which establishes an immune "memory". This programming enables heightened responsiveness to subsequent encounters with homologous or heterologous pathogens.[137,138] For example, Drosophila primed with low-pathogenicity bacteria exhibit markedly improved survival upon secondary challenge with virulent strains, illustrating conserved cross-protective mechanisms.[139] Immunostimulatory adjuvants targeting TLRs or other PRRs amplify Antigen-Presenting Cell (APC) activation and maturation, thereby enhancing antigen presentation and co-stimulatory signal generation to fortify innate immune efficacy[140,141] (Figure 2).

PRRs Regulate Trained Immunity Through the Interplay Between Metabolic Reprogramming and Epigenetics

PRRs are indispensable for immune cell activation and functional modulation. Emerging evidence demonstrates that PRRs not only drive classical immune signaling but also mediate trained immunity (TI) through crosstalk with metabolic and epigenetic networks.[142–144] TI is characterized by heightened immune responsiveness to secondary pathogenic challenges, driven by persistent metabolic and epigenetic adaptations following initial stimulatory events.[145,146] PRR signaling activates RNA polymerase II (RNPII) and Polycomb repressive complex 2 (PRC2), driving epigenetic modifications such as histone methylation (eg, H3K27me3) and acetylation to regulate the accessibility of pro-inflammatory and antiviral genes.[147,148] These processes are finely modulated by key metabolites including S-adenosylmethionine (SAM), acetyl-CoA, Nicotinamide Adenine Dinucleotide (NAD^+), and pyruvate. For instance, glucose and acetate-derived acetyl-CoA fuel the TCA cycle, altering metabolic flux dynamics to influence the NAD^+/ Nicotinamide Adenine Dinucleotide + Hydrogen (NADH) ratio, which activates deacetylases like Sirt1 to balance histone acetylation during inflammation resolution.[149,150] PRR activation induces metabolic rewiring in immune cells, reconfiguring energy utilization pathways. For example, macrophages undergo a metabolic switch from OXPHOS to aerobic glycolysis, rapidly generating ATP to sustain effector functions while modulating inflammatory polarization.[151,152] This glycolytic shift not only meets bioenergetic demands but also fuels epigenetic remodeling via metabolites such as acetyl-CoA and SAM.[153–155] Acetyl-CoA serves as a critical substrate for histone acetylation, amplifying acetylation levels to derepress cytokine genes (eg, *IL-6, TNF-α, IL-1β*), thereby potentiating pathogen-responsive capacity.[156] Beyond metabolic regulation, acetyl-CoA orchestrates inflammatory gene expression via a metabolic-epigenetic axis. TLR4 activation, for instance, upregulates glycolysis and tricarboxylic acid (TCA) cycle activity in macrophages, converting glucose-derived carbons into acetyl-CoA. This metabolite enhances histone acetylation

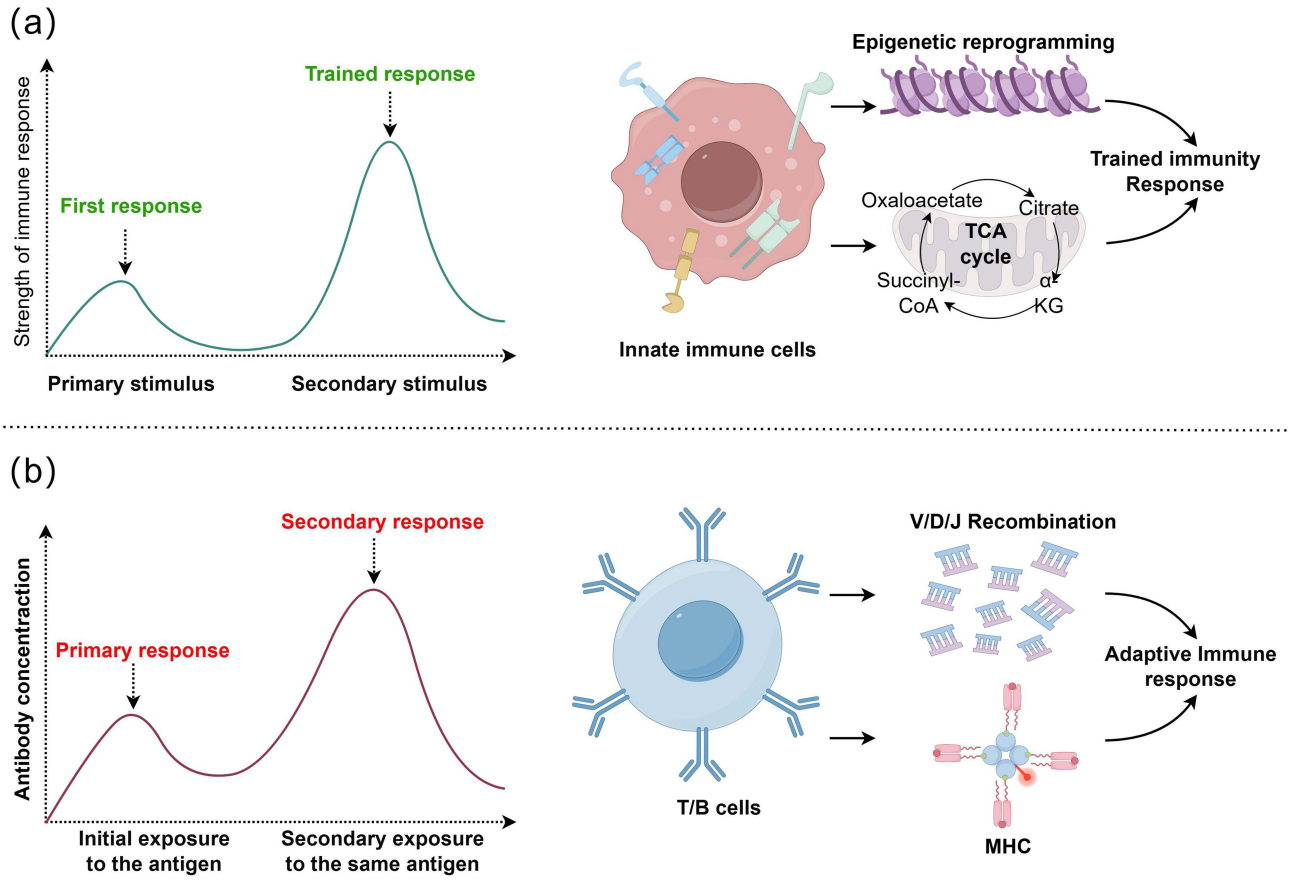

Figure 2 Comparison of trained immunity and adaptive immunity in immune responses. (**a**) Trained immunity: First exposure of innate immune cells to PAMPs induces a moderate initial response (first peak). Secondary challenge with heterologous stimuli triggers an amplified response (second peak), mediated by epigenetic modifications and metabolic shifts (enhanced glycolysis/TCA cycle activity). (**b**) Adaptive immunity: Antigen-specific recognition by T/B cells via TCR/BCR activates clonal expansion. Upon re-exposure to the same antigen, memory T/B cells rapidly proliferate and produce high-affinity antibodies (B cells) or cytokine/cytolytic responses (T cells). This memory relies on genetic recombination (V(D)J diversification in antigen receptors) and MHC-mediated antigen presentation to ensure specificity. (Created with Figdraw).

at loci encoding LPS-induced pro-inflammatory mediators (eg, *TNF-α, IL-6, NLRP3*), fine-tuning transcriptional outputs.[157]

Moreover, PRR signaling reprograms the epigenetic landscape of immune cells to synchronize metabolic plasticity with immunological memory. The SET domain-containing protein 7 (SET7) methyltransferase catalyzes monomethylation of H3K4me1, regulating both immune gene transcription and OXPHOS-associated metabolic pathways. Crucially, metabolic intermediates (eg, pyruvate) cooperate with epigenetic regulators (eg, AP-1, NF-κB) to amplify the expression of pro-inflammatory cytokines (eg, TNF-α, IL-6) and type I interferons (IFN-α/β), establishing a multi-layered immune response network.[158] Sustained OXPHOS-linked metabolic adjustments establish a "metabolic memory", enabling rapid reactivation of immune cells upon secondary pathogen encounters and reinforcing memory-driven protection.[159] The synergistic interplay between metabolic remodeling and epigenetic regulation underpins immediate immune effector functions and long-term adaptive priming. PRR-triggered metabolic-epigenetic integration thus emerges as a central mechanism for enhancing immune memory and shaping the pathogenesis of immune-mediated diseases (Figure 3).

https://doi.org/10.2147/JIR.S513325

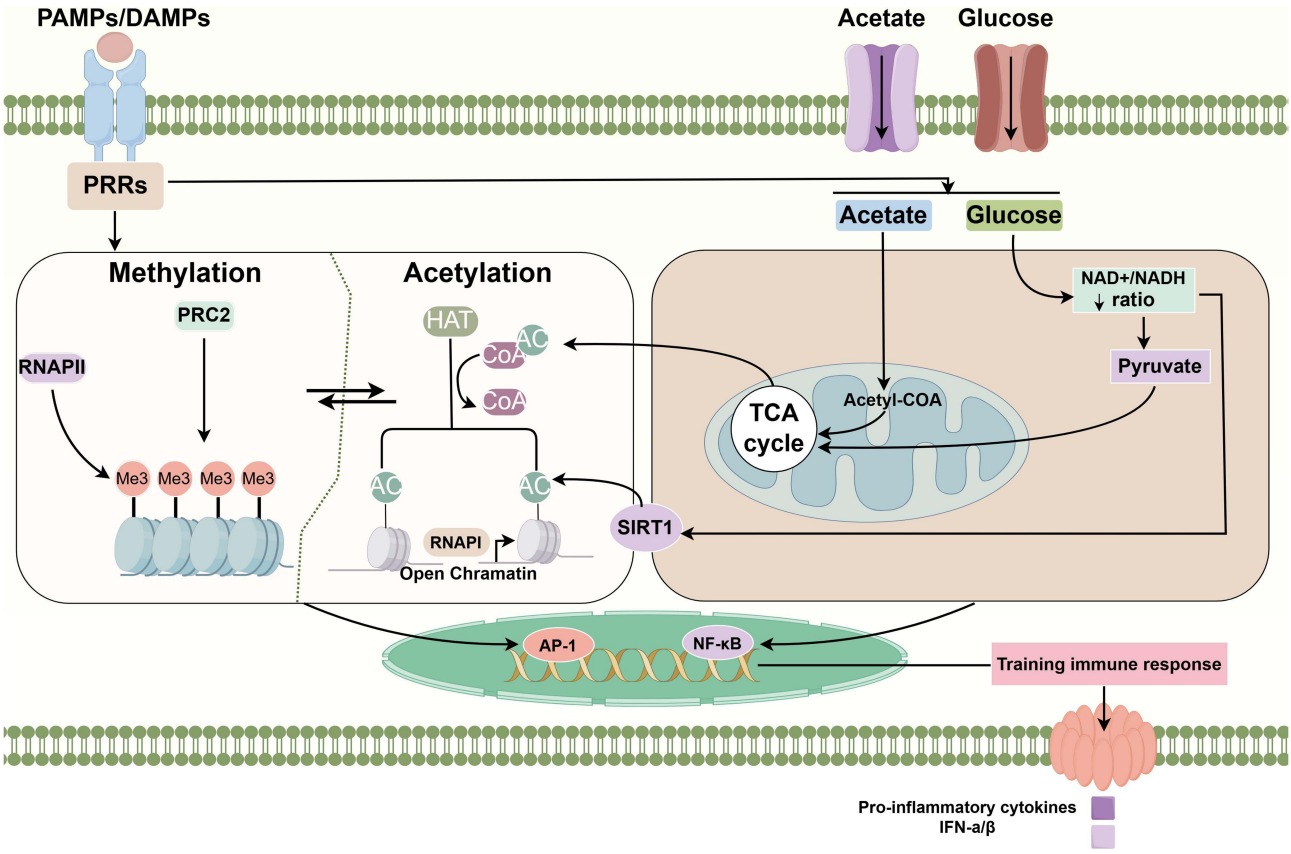

Figure 3 PRRs regulate trained immunity via epigenetic and metabolic reprogramming. Pathogen recognition via PRRs activates transcription machinery (eg, RNA polymerase II) and epigenetic modifiers (eg, Polycomb Repressive Complex 2, PRC2), inducing histone acetylation and methylation to prime immune gene loci. Key metabolites such as acetyl-CoA (generated from glucose and acetate), NAD+, and pyruvate fuel the TCA cycle, regulating the NAD+/NADH ratio and modulating sirtuin deacetylases (eg, Sirt1). These metabolic shifts synergize with chromatin remodeling to enhance transcriptional activation of *pro-inflammatory cytokines* (eg, IL-6, TNF-α) and type I interferons (IFN-α/β). Transcription factors (AP-1, NF-κB) further amplify immune gene expression, establishing a prolonged antimicrobial state. (Created with Figdraw).

Conclusion

TI, an adaptive memory-like response of innate immune cells, exhibits dualistic roles in host defense and pathological processes. This adaptive process proceeds through a hierarchical cascade: initial pathogen exposure triggers metabolic reprogramming (eg, glycolytic upregulation), yielding metabolites such as acetyl-CoA and α-ketoglutarate (α-KG), which serve as enzymatic cofactors for epigenetic remodeling, including histone acetylation and H3K4me1 deposition. These changes collectively prime immune cells for heightened responsiveness to secondary stimuli. Studies highlight TI's protective capacity; for example, dimethyl itaconate administration post-*Staphylococcus aureus* infection reprograms glycolytic and mitochondrial metabolism in murine models, enhancing microbial ligand sensitivity and survival outcomes.[160] Similarly, β-glucan-trained lung macrophages inhibit metastatic dissemination in preclinical tumor models.[161] However, emerging evidence cautions against unregulated TI activation, as maladaptive epigenetic reprogramming may fuel inflammatory pathology. Monocytes primed with LPS exhibit elevated H3K4me1 levels linked to exacerbated post-stroke inflammation, a process mitigated by mesenchymal stem cell therapy.[162] Furthermore, the gut microbiota-derived metabolite trimethylamine N-oxide (TMAO) enhances glycolytic flux via endoplasmic reticulum (ER) stress and ROS) signaling, exacerbating systemic inflammation.[163] TI dysregulation further contributes to chronic inflammatory diseases; in periodontitis and arthritis models, epigenetically driven myeloid cell differentiation sustains tissue destruction.[164] These findings underscore TI's context-dependent duality, wherein balanced activation enhances defense, whereas excessive engagement fuels pathogenesis.

Mechanistically, TI is categorized into central and peripheral subtypes. Central TI arises from epigenetic reprogramming of hematopoietic progenitors in the bone marrow or thymus, conferring enduring immune memory lasting months to years. Peripheral TI involves transient metabolic-epigenetic adaptations (weeks to months) in tissue-resident immune cells at sites of infection or injury.[165,166] Current TI inducers under investigation include LPS, β-glucan, and vaccines like Bacillus Calmette-Guérin (BCG).[167,168] LPS, a prototypical TLR4 agonist, is a widely studied TI inducer but risks immune tolerance or chronic inflammation due to hyperactivation.[169–171] Conversely, β-glucan enhances antifungal immunity by modulating dendritic cell (DC) function, though its capacity to maintain memory across heterogeneous microenvironments remains unclear.[172,173] BCG exemplifies a "training vaccine" with clinical promise, yet its mechanistic balance between protective priming and pathological immune hyperreactivity demands resolution.[174–176]

The regulatory centrality of PRRs in metabolic-epigenetic crosstalk is increasingly evident. PRR activation acts as a master regulator of immune cell plasticity, coordinating metabolic sensors (eg, mTOR, AMPK) and epigenetic modifiers (eg, HDACs, BET proteins) to establish cellular memory. To translate these insights into therapies, four research imperatives emerge: (1) Elucidating spatiotemporal dynamics of PRR-coupled signaling hubs linking pathogen sensing to chromatin accessibility and metabolic shifts; (2) Systematically defining tissue- and disease-specific modifiers (eg, hypoxia, microbiota metabolites) dictating TI outcomes; (3) Designing context-sensitive PRR modulators to balance glycolysis-TCA cycle flux without inducing metabolic exhaustion; (4) Longitudinal profiling of PRR-driven TI in chronic inflammation and aging to resolve its dual roles as protector and disease accelerator. In conclusion, TI redefines immune memory paradigms, transcending classical adaptive immunity frameworks. While PRR-targeted metabolic-epigenetic modulation offers therapeutic promise, maintaining long-term immune homeostasis remains paramount. Future research must prioritize precision platforms that reconcile the pleiotropic effects of PRR signaling across diverse pathological landscapes.

Abbreviations

PRRs, Pattern recognition receptors; TI, Trained immunity; TLRs, Toll-like receptors; CLRs, C-type lectin receptors; MAPK, Mitogen-Activated Protein Kinase; MyD88, Myeloid Differentiation Primary Response 88; TIR, Toll/Interleukin-1 Receptor; IRAK4, Interleukin-1 Receptor-Associated Kinase 4; IRAK1, Interleukin-1 Receptor-Associated Kinase 1; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; CARD9, Caspase Recruitment Domain Containing Protein 9; BCL10, B-cell Lymphoma 10; MALT1, Mucosa-Associated Lymphoid Tissue Lymphoma Translocation Protein 1; TAK1, TGF-beta-activated kinase 1; IκBα, Inhibitor of Nuclear Factor kappa-B alpha; CpG, cytosine-phosphate-guanine; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; LPS, lipopolysaccharide; CTL, cytotoxic T lymphocyte; CpG ODN, CpG oligodeoxynucleotides; NLRs, NOD-like receptors; CRDs, carbohydrate-recognition domains; RLRs, (RIG-I)-like receptors; MAVS, mitochondrial antiviral-signaling protein; DNMTs, DNA methyltransferases; HDAC, histone deacetylase; miRNAs, microRNAs; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; IRG1, immune-responsive gene 1; TAMs, tumor-associated macrophages; TET2, Tet methylcytosine dioxygenase 2; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PI3K, Phosphoinositide 3-kinase; AKT, Protein kinase B; JAK, Janus kinase; STAT, Signal Transducer and Activator of Transcription; NLRP3, NOD-like receptor family pyrin domain containing 3; JNK1, c-Jun N-terminal kinase 1; BRCC3, BRCA1-Associated Protein 1; AMPK, AMP-activated protein kinase; mTOR, Mammalian Target of Rapamycin; APC, Antigen-Presenting Cell; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; CH25H, cholesterol-25-hydroxylase; 25HC, 25-hydroxycholesterol; PKM2, Pyruvate Kinase M2; TME, tumor microenvironment; TILs, tumor-infiltrating T cells; NAD^+, Nicotinamide Adenine Dinucleotide; NADH, Nicotinamide Adenine Dinucleotide + Hydrogen; ACC, acetyl-CoA carboxylase; SCFAs, Short-chain fatty acids; RNPII, PRR signaling activates RNA polymerase II; PRC2, Polycomb repressive complex 2; SAM, S-adenosylmethionine; TCA, tricarboxylic acid; SET7, SET domain-containing protein 7; α-KG, α-ketoglutarate; TMAO, trimethylamine N-oxide; ER, endoplasmic reticulum; BCG, Bacillus Calmette-Guérin; DC, dendritic cell.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Acknowledgments

We are particularly grateful to all the people who have given us help on our article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The authors acknowledge financial support for the research, authorship, and/or publication of this article. This work was funded by the National Natural Science Foundation of China (Grant No. 82360200), the Provincial Innovation Team for Multidisciplinary Diagnosis and Treatment of Complex Craniomaxillofacial Malformations at the Affiliated Stomatology Hospital of Kunming Medical University (Grant No. 202105AE160004), the Yunnan Provincial Oral Disease Clinical Medical Research Center Scientific Research Fund (Grant No. 2022QN004), and the Yunnan Provincial Department of Science and Technology Kunming Medical Joint Special General Project (Grant No. 202301AY070001-062). Partial support was also provided by the First-Class Discipline Team of Kunming Medical University (Grant No. 2024XKTDTS08).

Disclosure

The authors declare that this research was conducted without any commercial or financial relationships that could be perceived as potential conflicts of interest.

References

1. Netea MG, Quintin J, van der Meer JM. Trained immunity: a memory for innate host defense. *Cell Host Microbe*. 2011;9(5):355–361. doi:10.1016/j.chom.2011.04.006
2. Netea MG, Joosten LAB, Latz E, et al. Trained immunity: a program of innate immune memory in health and disease. *Science*. 2016;352(6284): aaf1098. doi:10.1126/science.aaf1098
3. Wicherska-Pawłowska K, Wróbel T, Rybka J. Toll-Like Receptors (TLRs), NOD-Like Receptors (NLRs), and RIG-I-Like Receptors (RLRs) in innate immunity. TLRs, NLRs, and RLRs ligands as immunotherapeutic agents for hematopoietic diseases. *Int J Mol Sci*. 2021;22(24):13397. doi:10.3390/ijms222413397
4. Xu Z, Kombe Kombe AJ, Deng S, et al. NLRP inflammasomes in health and disease. *Mol Biomed*. 2024;5(1):14. doi:10.1186/s43556-024-00179-x
5. Lérias JR, de Sousa E, Paraschoudi G, et al. Trained immunity for personalized cancer immunotherapy: current knowledge and future opportunities. *Front Microbiol*. 2020;10:2924. doi:10.3389/fmicb.2019.02924
6. Sherwood ER, Burelbach KR, McBride MA, et al. Innate immune memory and the host response to infection. *J Immunol*. 2022;208 (4):785–792. doi:10.4049/jimmunol.2101058
7. Rosati D, Pradhan A, van Heck JIP, et al. Candida albicans N -Linked Mannans potentiate the induction of trained immunity via Dectin-2. *J Infect Dis*. 2024;230(3):768–777. doi:10.1093/infdis/jiae112
8. Xiong M-G, Xu Z-S, Li Y-H, et al. RNF 152 positively regulates TLR / IL −1R signaling by enhancing MyD88 oligomerization. *EMBO Rep*. 2020;21(3):e48860. doi:10.15252/embr.201948860
9. Barrera M-J, Aguilera S, Castro I, et al. Dysfunctional mitochondria as critical players in the inflammation of autoimmune diseases: potential role in Sjögren's syndrome. *Autoimmun Rev*. 2021;20(8):102867. doi:10.1016/j.autrev.2021.102867
10. Khader SA, Divangahi M, Hanekom W, et al. Targeting innate immunity for tuberculosis vaccination. *J Clin Investig*. 2019;129(9):3482–3491. doi:10.1172/jci128877
11. Domínguez-Andrés J, Dos Santos JC, Bekkering S, et al. Trained immunity: adaptation within innate immune mechanisms. *Physiol Rev*. 2023;103(1):313–346. doi:10.1152/physrev.00031.2021
12. Bhargavi G, Subbian S. The causes and consequences of trained immunity in myeloid cells. *Front Immunol*. 2024;15:1365127. doi:10.3389/fimmu.2024.1365127
13. Patil SU, Shreffler WG. Novel vaccines: technology and development. *J Allergy Clin Immunol*. 2019;143(3):844–851. doi:10.1016/j.jaci.2018.05.021
14. Merimi M, Buyl K, Daassi D, et al. Transcriptional profile of cytokines, regulatory mediators and TLR in mesenchymal stromal cells after inflammatory signaling and cell-passaging. *Int J Mol Sci*. 2021;22(14):7309. doi:10.3390/ijms22147309
15. Du Y, Ah Kioon MD, Laurent P, et al. Chemokines form nanoparticles with DNA and can superinduce TLR-driven immune inflammation. *J Exp Med*. 2022;219(7). doi:10.1084/jem.20212142

16. Zhang L, Wei X, Wang Z, et al. NF-κB activation enhances STING signaling by altering microtubule-mediated STING trafficking. *Cell Rep*. 2023;42(3):112185. doi:10.1016/j.celrep.2023.112185
17. Rodríguez A, Velázquez J, González L, et al. PACAP modulates the transcription of TLR-1/TLR-5/MyD88 pathway genes and boosts antimicrobial defenses in Clarias gariepinus. *Fish Shellfish Immunol*. 2021;115:150–159. doi:10.1016/j.fsi.2021.06.009
18. Lee KM, Fu Q, Huai G, et al. Suppression of allograft rejection by regulatory B cells induced via TLR signaling. *JCI Insight*. 2022;7(17). doi:10.1172/jci.insight.152213
19. Chang LS, Leng CH, Yeh YC, et al. Toll-like receptor 9 agonist enhances anti-tumor immunity and inhibits tumor-associated immunosuppressive cells numbers in a mouse cervical cancer model following recombinant lipoprotein therapy. *Mol Cancer*. 2014;13:60. doi:10.1186/1476-4598-13-60
20. Dar AA, Patil RS, Chiplunkar SV. Insights into the relationship between toll like receptors and gamma delta T cell responses. *Front Immunol*. 2014;5:366. doi:10.3389/fimmu.2014.00366
21. Li J, Yang F, Wei F, et al. The role of toll-like receptor 4 in tumor microenvironment. *Oncotarget*. 2017;8(39):66656–66667. doi:10.18632/oncotarget.19105
22. Barbé F, Douglas T, Saleh M. Advances in Nod-like receptors (NLR) biology. *Cytokine Growth Factor Rev*. 2014;25(6):681–697. doi:10.1016/j.cytogfr.2014.07.001
23. Godkowicz M, Druszczyńska M. NOD1, NOD2, and NLRC5 receptors in antiviral and antimycobacterial immunity. *Vaccines*. 2022;10(9). doi:10.3390/vaccines10091487
24. Clarke TB, Weiser JN. Intracellular sensors of extracellular bacteria. *Immunol Rev*. 2011;243(1):9–25. doi:10.1111/j.1600-065X.2011.01039.x
25. Kasimsetty SG, Shigeoka AA, Scheinok AA, et al. Lack of both nucleotide-binding oligomerization domain-containing proteins 1 and 2 primes T cells for activation-induced cell death. *J Immunol*. 2017;199(3):1196–1205. doi:10.4049/jimmunol.1600667
26. Li YY, Pearson JA, Chao C, et al. Nucleotide-binding oligomerization domain-containing protein 2 (Nod2) modulates T1DM susceptibility by gut microbiota. *J Autoimmun*. 2017;82:85–95. doi:10.1016/j.jaut.2017.05.007
27. Yamaguchi N, Suzuki Y, Mahbub MH, et al. The different roles of innate immune receptors in inflammation and carcinogenesis between races. *Environ Health Prevent Med*. 2017;22(1):70. doi:10.1186/s12199-017-0678-8
28. Conos SA, Lawlor KE, Vaux DL, et al. Cell death is not essential for caspase-1-mediated interleukin-1β activation and secretion. *Cell Death Differentiation*. 2016;23(11):1827–1838. doi:10.1038/cdd.2016.69
29. Kearns AC, Robinson JA, Shekarabi M, et al. Caspase-1-associated immune activation in an accelerated SIV-infected rhesus macaque model. *J Neurovirol*. 2018;24(4):420–431. doi:10.1007/s13365-018-0630-8
30. Zheng J, Hu Q, Zou X, et al. Uranium induces kidney cells pyroptosis in culture involved in ROS/NLRP3/caspase-1 signaling. *Free Radical Res*. 2022;56(1):40–52. doi:10.1080/10715762.2022.2032021
31. Kim YK, Shin JS, Nahm MH. NOD-like receptors in infection, immunity, and diseases. *Yonsei Med J*. 2016;57(1):5–14. doi:10.3349/ymj.2016.57.1.5
32. Takagi M, Takakubo Y, Pajarinen J, et al. Danger of frustrated sensors: role of toll-like receptors and NOD-like receptors in aseptic and septic inflammations around total hip replacements. *J Orthopaed Transl*. 2017;10:68–85. doi:10.1016/j.jot.2017.05.004
33. Ohto U. Activation and regulation mechanisms of NOD-like receptors based on structural biology. *Front Immunol*. 2022;13:953530. doi:10.3389/fimmu.2022.953530
34. Kong X, Yuan Z, Cheng J. The function of NOD-like receptors in central nervous system diseases. *J Neurosci Res*. 2017;95(8):1565–1573. doi:10.1002/jnr.24004
35. Toldo S, Mezzaroma E, Buckley LF, et al. Targeting the NLRP3 inflammasome in cardiovascular diseases. *Pharmacol Therap*. 2022;236:108053. doi:10.1016/j.pharmthera.2021.108053
36. Plato A, Hardison SE, Brown GD. Pattern recognition receptors in antifungal immunity. *Seminars Immunopathol*. 2015;37(2):97–106. doi:10.1007/s00281-014-0462-4
37. Goyal S, Castrillón-Betancur JC, Klaile E, et al. The interaction of human pathogenic fungi with C-type lectin receptors. *Front Immunol*. 2018;9:1261. doi:10.3389/fimmu.2018.01261
38. Li K, Underhill DM. C-type lectin receptors in phagocytosis. *Curr Topics Microbiol Immunol*. 2020;429:1–18. doi:10.1007/82_2020_198
39. Nikolakopoulou C, Willment JA, Brown GD. C-type lectin receptors in antifungal immunity. *Adv Exp Med Biol*. 2020;1204:1–30. doi:10.1007/978-981-15-1580-4_1
40. Bao MY, Li M, Bu QR, et al. The effect of herbal medicine in innate immunity to Candida albicans. *Front Immunol*. 2023;14:1096383. doi:10.3389/fimmu.2023.1096383
41. Monteiro JT, Lepenies B. Myeloid C-type lectin receptors in viral recognition and antiviral immunity. *Viruses*. 2017;9(3). doi:10.3390/v9030059
42. Shiokawa M, Yamasaki S, Saijo S. C-type lectin receptors in anti-fungal immunity. *Curr Opin Microbiol*. 2017;40:123–130. doi:10.1016/j.mib.2017.11.004
43. Drouin M, Saenz J, Chiffoleau E. C-type lectin-like receptors: head or tail in cell death immunity. *Front Immunol*. 2020;11:251. doi:10.3389/fimmu.2020.00251
44. Li Q. The multiple roles of C-type lectin receptors in cancer. *Front Oncol*. 2023;13:1301473. doi:10.3389/fonc.2023.1301473
45. Yan H, Kamiya T, Suabjakyong P, et al. Targeting C-type lectin receptors for cancer immunity. *Front Immunol*. 2015;6:408. doi:10.3389/fimmu.2015.00408
46. Sionov RV, Lamagna C, Granot Z. Recognition of tumor nidogen-1 by neutrophil C-type lectin receptors. *Biomedicines*. 2022;10(4). doi:10.3390/biomedicines10040908
47. Lian H, Zang R, Wei J, et al. The zinc-finger protein ZCCHC3 binds RNA and facilitates viral RNA sensing and activation of the RIG-I-like receptors. *Immunity*. 2018;49(3):438–448.e435. doi:10.1016/j.immuni.2018.08.014
48. Wang X, Lin L, Chen Z, et al. Mutations at site 207 of influenza a virus NS1 protein switch its function in regulating RIG-I-like receptors mediated antiviral responses. *Antiviral Res*. 2023;215:105641. doi:10.1016/j.antiviral.2023.105641
49. Ma J, Ketkar H, Geng T, et al. Zika virus non-structural protein 4A blocks the RLR-MAVS signaling. *Front Microbiol*. 2018;9:1350. doi:10.3389/fmicb.2018.01350

50. Solotchi M, Patel SS. Proofreading mechanisms of the innate immune receptor RIG-I: distinguishing self and viral RNA. *Biochem Soc Transact*. 2024;52(3):1131–1148. doi:10.1042/bst20230724
51. Krchlíková V, Hron T, Těšický M, et al. Dynamic evolution of Avian RNA virus sensors: repeated loss of RIG-I and RIPLET. *Viruses*. 2022;15 (1). doi:10.3390/v15010003
52. Oshikawa D, Inaba S, Kitagawa Y, et al. CpG methylation altered the stability and structure of the i-Motifs located in the CpG Islands. *Int J Mol Sci*. 2022;23(12). doi:10.3390/ijms23126467
53. Sergeeva A, Davydova K, Perenkov A, et al. Mechanisms of human DNA methylation, alteration of methylation patterns in physiological processes and oncology. *Gene*. 2023;875:147487. doi:10.1016/j.gene.2023.147487
54. Nishiyama A, Nakanishi M. Navigating the DNA methylation landscape of cancer. *Trends Genetics*. 2021;37(11):1012–1027. doi:10.1016/j.tig.2021.05.002
55. Raciti GA, Desiderio A, Longo M, et al. DNA methylation and type 2 diabetes: novel biomarkers for risk assessment? *Int J Mol Sci*. 2021;22 (21). doi:10.3390/ijms222111652
56. Hu S, Chen L, Zeng T, et al. DNA methylation profiling reveals novel pathway implicated in cardiovascular diseases of diabetes. *Front Endocrinol*. 2023;14:1108126. doi:10.3389/fendo.2023.1108126
57. Ji H, Li K, Jiang W, et al. MRVI1 and NTRK3 are potential tumor suppressor genes commonly inactivated by DNA methylation in cervical cancer. *Front Oncol*. 2021;11:802068. doi:10.3389/fonc.2021.802068
58. Ma L, Li C, Yin H, et al. The mechanism of DNA methylation and miRNA in breast cancer. *Int J Mol Sci*. 2023;24(11). doi:10.3390/ijms24119360
59. Chen Z, Zhang Y. Role of mammalian DNA methyltransferases in development. *Ann Rev Biochem*. 2020;89:135–158. doi:10.1146/annurev-biochem-103019-102815
60. Klupczyńska EA, Ratajczak E. Can forest trees cope with climate change?-Effects of DNA methylation on gene expression and adaptation to environmental change. *Int J Mol Sci*. 2021;22(24). doi:10.3390/ijms222413524
61. Bai L, Hao X, Keith J, et al. DNA methylation in regulatory T cell differentiation and function: challenges and opportunities. *Biomolecules*. 2022;12(9). doi:10.3390/biom12091282
62. Rauluseviciute I, Drabløs F, Rye MB. DNA methylation data by sequencing: experimental approaches and recommendations for tools and pipelines for data analysis. *Clinical Epigenetics*. 2019;11(1):193. doi:10.1186/s13148-019-0795-x
63. Liu F, Wang Y, Gu H, et al. Technologies and applications of single-cell DNA methylation sequencing. *Theranostics*. 2023;13(8):2439–2454. doi:10.7150/thno.82582
64. Nakato R, Sakata T. Methods for ChIP-seq analysis: a practical workflow and advanced applications. *Methods*. 2021;187:44–53. doi:10.1016/j.ymeth.2020.03.005
65. Li H, Li D, Humphreys BD. Chromatin conformation and histone modification profiling across human kidney anatomic regions. *Scientific Data*. 2024;11(1):797. doi:10.1038/s41597-024-03648-8
66. Lee SC, Adams DW, Ipsaro JJ, et al. Chromatin remodeling of histone H3 variants by DDM1 underlies epigenetic inheritance of DNA methylation. *Cell*. 2023;186(19):4100–4116.e4115. doi:10.1016/j.cell.2023.08.001
67. Shi W, Cassmann TJ, Bhagwate AV, et al. Lactic acid induces transcriptional repression of macrophage inflammatory response via histone acetylation. *Cell Rep*. 2024;43(2):113746. doi:10.1016/j.celrep.2024.113746
68. Ferrand J, Plessier A, Polo SE. Control of the chromatin response to DNA damage: histone proteins pull the strings. *Seminars Cell Develop Biol*. 2021;113:75–87. doi:10.1016/j.semcdb.2020.07.002
69. Lu C, Coradin M, Janssen KA, et al. Combinatorial histone H3 modifications are dynamically altered in distinct cell cycle phases. *J Am Soc Mass Spectrometry*. 2021;32(6):1300–1311. doi:10.1021/jasms.0c00451
70. Yu J, Chai P, Xie M, et al. Histone lactylation drives oncogenesis by facilitating m(6)A reader protein YTHDF2 expression in ocular melanoma. *Genome Biol*. 2021;22(1):85. doi:10.1186/s13059-021-02308-z
71. Yang Y, Zhang M, Wang Y. The roles of histone modifications in tumorigenesis and associated inhibitors in cancer therapy. *J Natl Cancer Center*. 2022;2(4):277–290. doi:10.1016/j.jncc.2022.09.002
72. Feng J, Meng X. Histone modification and histone modification-targeted anti-cancer drugs in breast cancer: fundamentals and beyond. *Front Pharmacol*. 2022;13:946811. doi:10.3389/fphar.2022.946811
73. Han TS, Hur K, Cho HS, et al. Epigenetic associations between lncRNA/circRNA and miRNA in hepatocellular carcinoma. *Cancers*. 2020;12 (9). doi:10.3390/cancers12092622
74. Yan H, Bu P. Non-coding RNA in cancer. *Essays Biochem*. 2021;65(4):625–639. doi:10.1042/ebc20200032
75. Do DN, Suravajhala P. Editorial: role of non-coding RNAs in animals. *Animals*. 2023;13(5). doi:10.3390/ani13050805
76. Biasini A, Abdulkarim B, de Pretis S, et al. Translation is required for miRNA-dependent decay of endogenous transcripts. *EMBO J*. 2021;40 (3):e104569. doi:10.15252/embj.2020104569
77. Qi Y, Ding L, Zhang S, et al. A plant immune protein enables broad antitumor response by rescuing microRNA deficiency. *Cell*. 2022;185 (11):1888–1904.e1824. doi:10.1016/j.cell.2022.04.030
78. Zhang G, Zhang X, Zhou K, et al. miRNA-10a-5p targeting the BCL6 gene regulates proliferation, differentiation and apoptosis of chicken myoblasts. *Int J Mol Sci*. 2022;23(17). doi:10.3390/ijms23179545
79. Fan Y, Ren C, Deng K, et al. The regulation of LncRNA GTL2 expression by DNA methylation during sheep skeletal muscle development. *Genomics*. 2022;114(5):110453. doi:10.1016/j.ygeno.2022.110453
80. Liu S, Zhou J, Ye X, et al. A novel lncRNA SNHG29 regulates EP300- related histone acetylation modification and inhibits FLT3-ITD AML development. *Leukemia*. 2023;37(7):1421–1434. doi:10.1038/s41375-023-01923-y
81. Zhao C, Gan C, Xiao Y, et al. High expression of long non-coding RNA Linc-A associates with poor survival in patients with colorectal cancer. *Mol Biol Rep*. 2020;47(10):7497–7504. doi:10.1007/s11033-020-05809-5
82. Sun J, Zhou F, Xue J, et al. Long non-coding RNA TRPM2-AS regulates microRNA miR-138-5p and PLAU (Plasminogen Activator, Urokinase) to promote the progression of gastric adenocarcinoma. *Bioengineered*. 2021;12(2):9753–9765. doi:10.1080/21655979.2021.1995101
83. Faraldi M, Gomarasca M, Yin C, et al. Editorial: role of long non-coding RNA and Circular RNA in bone metabolism and their role as circulating biomarkers for bone diseases. *Front Endocrinol*. 2023;14:1321962. doi:10.3389/fendo.2023.1321962

84. Szeto CC, So H, Poon PY, et al. Urinary Long non-coding RNA levels as biomarkers of Lupus nephritis. *Int J Mol Sci*. 2023;24(14). doi:10.3390/ijms241411813
85. Paulmurugan R, Malhotra M, Massoud TF. The protean world of non-coding RNAs in glioblastoma. *J Mol Med*. 2019;97(7):909–925. doi:10.1007/s00109-019-01798-6
86. Ardiana M, Fadila AN, Zuhra Z, et al. Non-coding RNA therapeutics in cardiovascular diseases and risk factors: systematic review. *Non-Coding RNA Res*. 2023;8(4):487–506. doi:10.1016/j.ncrna.2023.06.002
87. Suri C, Swarnkar S, Bhaskar L, et al. Non-Coding RNA as a biomarker in lung cancer. *Non-Coding RNA*. 2024;10(5). doi:10.3390/ncrna10050050
88. Li X, Ye Y, Peng K, et al. Histones: the critical players in innate immunity. *Front Immunol*. 2022;13:1030610. doi:10.3389/fimmu.2022.1030610
89. Cooke JP, Lai L. Transflammation in tissue regeneration and response to injury: how cell-autonomous inflammatory signaling mediates cell plasticity. *Adv Drug Deliv Rev*. 2023;203:115118. doi:10.1016/j.addr.2023.115118
90. Li X, Li X, Huang P, et al. Acetylation of TIR domains in the TLR4-Mal-MyD88 complex regulates immune responses in sepsis. *EMBO J*. 2024;43(21):4954–4983. doi:10.1038/s44318-024-00237-8
91. Czimmerer Z, Halasz L, Daniel B, et al. The epigenetic state of IL-4-polarized macrophages enables inflammatory cistromic expansion and extended synergistic response to TLR ligands. *Immunity*. 2022;55(11):2006–2026.e2006. doi:10.1016/j.immuni.2022.10.004
92. Huang M, Malovic E, Ealy A, et al. Microglial immune regulation by epigenetic reprogramming through histone H3K27 acetylation in neuroinflammation. *Front Immunol*. 2023;14:1052925. doi:10.3389/fimmu.2023.1052925
93. Yalcinkaya M, Liu W, Thomas LA, et al. BRCC3-mediated NLRP3 deubiquitylation promotes inflammasome activation and atherosclerosis in Tet2 clonal hematopoiesis. *Circulation*. 2023;148(22):1764–1777. doi:10.1161/circulationaha.123.065344
94. Saeed S, Quintin J, Kerstens HH, et al. Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. *Science*. 2014;345(6204):1251086. doi:10.1126/science.1251086
95. Ghanavatinejad A, Rashidi N, Mirahmadian M, et al. Vitamin D3 controls TLR4- and TLR2-mediated inflammatory responses of endometrial cells. *Gynecologic Obstetric Investig*. 2021;86(1–2):139–148. doi:10.1159/000513590
96. Kosinsky RL, Zerche M, Kutschat AP, et al. RNF20 and RNF40 regulate vitamin D receptor-dependent signaling in inflammatory bowel disease. *Cell Death Differentiation*. 2021;28(11):3161–3175. doi:10.1038/s41418-021-00808-w
97. Samson A, Scott KJ, Taggart D, et al. Intravenous delivery of oncolytic reovirus to brain tumor patients immunologically primes for subsequent checkpoint blockade. *Sci Transl Med*. 2018;10(422). doi:10.1126/scitranslmed.aam7577
98. Sagiv-Barfi I, Czerwinski DK, Levy S, et al. Eradication of spontaneous malignancy by local immunotherapy. *Sci Transl Med*. 2018;10(426). doi:10.1126/scitranslmed.aan4488
99. Lobb RJ, Visan KS, Wu LY, et al. An epithelial-to-mesenchymal transition induced extracellular vesicle prognostic signature in non-small cell lung cancer. *Commun Biol*. 2023;6(1):68. doi:10.1038/s42003-022-04350-4
100. Purdy JG, Luftig MA. Reprogramming of cellular metabolic pathways by human oncogenic viruses. *Curr Opinion Virol*. 2019;39:60–69. doi:10.1016/j.coviro.2019.11.002
101. Chakraborty S, Balan M, Sabarwal A, et al. Metabolic reprogramming in renal cancer: events of a metabolic disease. *Biochimica Et Biophysica Acta Reviews on Cancer*. 2021;1876(1):188559. doi:10.1016/j.bbcan.2021.188559
102. Li YJ, Zhang C, Martincuks A, et al. STAT proteins in cancer: orchestration of metabolism. *Nat Rev Cancer*. 2023;23(3):115–134. doi:10.1038/s41568-022-00537-3
103. Lu J, Tan M, Cai Q. The Warburg effect in tumor progression: mitochondrial oxidative metabolism as an anti-metastasis mechanism. *Cancer Lett*. 2015;356(2 Pt A):156–164. doi:10.1016/j.canlet.2014.04.001
104. Jin Y, Cai Q, Shenoy AK, et al. Src drives the Warburg effect and therapy resistance by inactivating pyruvate dehydrogenase through tyrosine-289 phosphorylation. *Oncotarget*. 2016;7(18):25113–25124. doi:10.18632/oncotarget.7159
105. Lu J. The Warburg metabolism fuels tumor metastasis. *Cancer Metastasis Rev*. 2019;38(1–2):157–164. doi:10.1007/s10555-019-09794-5
106. Jing C, Castro-Dopico T, Richoz N, et al. Macrophage metabolic reprogramming presents a therapeutic target in lupus nephritis. *Proc Natl Acad Sci U S A*. 2020;117(26):15160–15171. doi:10.1073/pnas.2000943117
107. Aso K, Kono M, Kanda M, et al. Itaconate ameliorates autoimmunity by modulating T cell imbalance via metabolic and epigenetic reprogramming. *Nat Commun*. 2023;14(1):984. doi:10.1038/s41467-023-36594-x
108. Tharp KM, Kersten K, Maller O, et al. Tumor-associated macrophages restrict CD8(+) T cell function through collagen deposition and metabolic reprogramming of the breast cancer microenvironment. *Nat Cancer*. 2024;5(7):1045–1062. doi:10.1038/s43018-024-00775-4
109. Li D, Wu M. Pattern recognition receptors in health and diseases. *Signal Transduct Target Ther*. 2021;6(1):291. doi:10.1038/s41392-021-00687-0
110. Ren M, Zheng X, Gao H, et al. Nanomedicines targeting metabolism in the tumor microenvironment. *Front Bioeng Biotechnol*. 2022;10:943906. doi:10.3389/fbioe.2022.943906
111. Ramnath D, Das Gupta K, Wang Y, et al. The histone deacetylase Hdac7 supports LPS-inducible glycolysis and Il-1β production in murine macrophages via distinct mechanisms. *J Leukocyte Biol*. 2022;111(2):327–336. doi:10.1002/jlb.2mr1021-260r
112. Vaez H, Soraya H, Garjani A, et al. Toll-Like Receptor 4 (TLR4) and AMPK relevance in cardiovascular disease. *Adv Pharm Bull*. 2023;13(1):36–47. doi:10.34172/apb.2023.004
113. Park S, Kim G, Choi A, et al. Comparative network-based analysis of toll-like receptor agonist, L-pampo signaling pathways in immune and cancer cells. *Sci Rep*. 2024;14(1):17173. doi:10.1038/s41598-024-67000-1
114. Kumar V, Stewart Iv JH. Pattern-recognition receptors and immunometabolic reprogramming: what we know and what to explore. *J Innate Immun*. 2024;16(1):295–323. doi:10.1159/000539278
115. Punekar S, Cho DC. Novel therapeutics affecting metabolic pathways. *Am Soc Clin Oncol Educ Book Am Soc Clin Oncol Ann Meet*. 2019;39:e79–e87. doi:10.1200/edbk_238499
116. Egan G, Khan DH, Lee JB, et al. Mitochondrial and metabolic pathways regulate nuclear gene expression to control differentiation, stem cell function, and immune response in Leukemia. *Cancer Discov*. 2021;11(5):1052–1066. doi:10.1158/2159-8290.Cd-20-1227
117. Wu D. Innate and adaptive immune cell metabolism in tumor microenvironment. *Adv Exp Med Biol*. 2017;1011:211–223. doi:10.1007/978-94-024-1170-6_7

118. Ratter JM, Tack CJ, Netea MG, et al. Environmental signals influencing myeloid cell metabolism and function in diabetes. *Trends Endocrinol Metabol*. 2018;29(7):468–480. doi:10.1016/j.tem.2018.04.008
119. Hu C, Xuan Y, Zhang X, et al. Immune cell metabolism and metabolic reprogramming. *Mol Biol Rep*. 2022;49(10):9783–9795. doi:10.1007/s11033-022-07474-2
120. Wang J, Yang P, Yu T, et al. Lactylation of PKM2 suppresses inflammatory metabolic adaptation in pro-inflammatory macrophages. *Int J Biol Sci*. 2022;18(16):6210–6225. doi:10.7150/ijbs.75434
121. Xiao J, Wang S, Chen L, et al. 25-Hydroxycholesterol regulates lysosome AMP kinase activation and metabolic reprogramming to educate immunosuppressive macrophages. *Immunity*. 2024;57(5):1087–1104.e1087. doi:10.1016/j.immuni.2024.03.021
122. Adamik J, Munson PV, Hartmann FJ, et al. Distinct metabolic states guide maturation of inflammatory and tolerogenic dendritic cells. *Nat Commun*. 2022;13(1):5184. doi:10.1038/s41467-022-32849-1
123. Harmon C, O'Farrelly C, Robinson MW. The immune consequences of lactate in the tumor microenvironment. *Adv Exper Med Biol*. 2020;1259:113–124. doi:10.1007/978-3-030-43093-1_7
124. Huang Y, Wang HC, Zhao J, et al. Immunosuppressive roles of Galectin-1 in the tumor microenvironment. *Biomolecules*. 2021;11(10). doi:10.3390/biom11101398
125. Madsen HB, Peeters MJ, Straten PT, et al. Nucleotide metabolism in the regulation of tumor microenvironment and immune cell function. *Curr Opin Biotechnol*. 2023;84:103008. doi:10.1016/j.copbio.2023.103008
126. Villalba M, Rathore MG, Lopez-Royuela N, et al. From tumor cell metabolism to tumor immune escape. *Int J Biochem Cell Biol*. 2013;45(1):106–113. doi:10.1016/j.biocel.2012.04.024
127. Ma G, Li C, Zhang Z, et al. Targeted glucose or glutamine metabolic therapy combined with PD-1/PD-L1 checkpoint blockade immunotherapy for the treatment of tumors - mechanisms and strategies. *Front Oncol*. 2021;11:697894. doi:10.3389/fonc.2021.697894
128. Park J, Hsueh PC, Li Z, et al. Microenvironment-driven metabolic adaptations guiding CD8(+) T cell anti-tumor immunity. *Immunity*. 2023;56(1):32–42. doi:10.1016/j.immuni.2022.12.008
129. Hunt EG, Hurst KE, Riesenberg BP, et al. Acetyl-CoA carboxylase obstructs CD8(+) T cell lipid utilization in the tumor microenvironment. *Cell Metabolism*. 2024;36(5):969–983.e910. doi:10.1016/j.cmet.2024.02.009
130. Li S, Yu J, Huber A, et al. Metabolism drives macrophage heterogeneity in the tumor microenvironment. *Cell Rep*. 2022;39(1):110609. doi:10.1016/j.celrep.2022.110609
131. Trompette A, Gollwitzer ES, Pattaroni C, et al. Dietary fiber confers protection against flu by shaping Ly6c(-) Patrolling monocyte hematopoiesis and CD8(+) T cell metabolism. *Immunity*. 2018;48(5):992–1005.e1008. doi:10.1016/j.immuni.2018.04.022
132. Christ A, Günther P, Lauterbach MAR, et al. Western diet triggers NLRP3-dependent innate immune reprogramming. *Cell*. 2018;172(1–2):162–175.e114. doi:10.1016/j.cell.2017.12.013
133. Patin EC, Thompson A, Orr SJ. Pattern recognition receptors in fungal immunity. *Seminars Cell Develop Biol*. 2019;89:24–33. doi:10.1016/j.semcdb.2018.03.003
134. Carroll SL, Pasare C, Barton GM. Control of adaptive immunity by pattern recognition receptors. *Immunity*. 2024;57(4):632–648. doi:10.1016/j.immuni.2024.03.014
135. Xie XD, Tang M, L YS, et al. Polysaccharide of Asparagus cochinchinensis (Lour.) Merr regulates macrophage immune response and epigenetic memory through TLR4-JNK/p38/ERK signaling pathway and histone modification. *Phytomedicine*. 2024;124:155294. doi:10.1016/j.phymed.2023.155294
136. Steevels TA, Meyaard L. Immune inhibitory receptors: essential regulators of phagocyte function. *Eur J Immunol*. 2011;41(3):575–587. doi:10.1002/eji.201041179
137. Reimer-Michalski EM, Conrath U. Innate immune memory in plants. *Seminars Immunol*. 2016;28(4):319–327. doi:10.1016/j.smim.2016.05.006
138. Ferreira AV, Domiguéz-Andrés J, Netea MG. The role of cell metabolism in innate immune memory. *J Innate Immun*. 2022;14(1):42–50. doi:10.1159/000512280
139. Tang C, Kurata S, Fuse N. Genetic dissection of innate immune memory in Drosophila melanogaster. *Front Immunol*. 2022;13:857707. doi:10.3389/fimmu.2022.857707
140. Pulendran B, A PS, O'Hagan DT. Emerging concepts in the science of vaccine adjuvants. *Nat Rev Drug Discov*. 2021;20(6):454–475. doi:10.1038/s41573-021-00163-y
141. Zhao T, Cai Y, Jiang Y, et al. Vaccine adjuvants: mechanisms and platforms. *Signal Transduct Target Ther*. 2023;8(1):283. doi:10.1038/s41392-023-01557-7
142. Owen AM, Fults JB, Patil NK, et al. TLR agonists as mediators of trained immunity: mechanistic insight and immunotherapeutic potential to combat infection. *Front Immunol*. 2020;11:622614. doi:10.3389/fimmu.2020.622614
143. Muñoz-Wolf N, Lavelle EC. Promotion of trained innate immunity by nanoparticles. *Seminars Immunol*. 2021;56:101542. doi:10.1016/j.smim.2021.101542
144. Petrof BJ, Podolsky T, Bhattarai S, et al. Trained immunity as a potential target for therapeutic immunomodulation in Duchenne muscular dystrophy. *Front Immunol*. 2023;14:1183066. doi:10.3389/fimmu.2023.1183066
145. Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol*. 2020;20(6):375–388. doi:10.1038/s41577-020-0285-6
146. Ochando J, Mulder WJM, Madsen JC, et al. Trained immunity - basic concepts and contributions to immunopathology. *Nat Rev Nephrol*. 2023;19(1):23–37. doi:10.1038/s41581-022-00633-5
147. Qu Y, Yang Q, Liu J, et al. c-Myc is Required for BRAF(V600E)-Induced Epigenetic Silencing by H3K27me3 in Tumorigenesis. *Theranostics*. 2017;7(7):2092–2107. doi:10.7150/thno.19884
148. Chen J, Liang X, Zhang S, et al. Two faces of bivalent domain regulate VEGFA responsiveness and angiogenesis. *Cell Death Dis*. 2020;11(1):75. doi:10.1038/s41419-020-2228-3
149. Li HR, Liu Q, Zhu CL, et al. β-Nicotinamide mononucleotide activates NAD+/SIRT1 pathway and attenuates inflammatory and oxidative responses in the hippocampus regions of septic mice. *Redox Biol*. 2023;63:102745. doi:10.1016/j.redox.2023.102745
150. Yu H, Gan D, Luo Z, et al. α-Ketoglutarate improves cardiac insufficiency through NAD(+)-SIRT1 signaling-mediated mitophagy and ferroptosis in pressure overload-induced mice. *Mol Med*. 2024;30(1):15. doi:10.1186/s10020-024-00783-1

151. Ye L, Jiang Y, Zhang M. Crosstalk between glucose metabolism, lactate production and immune response modulation. *Cytokine Growth Factor Rev*. 2022;68:81–92. doi:10.1016/j.cytogfr.2022.11.001
152. Wculek SK, Heras-Murillo I, Mastrangelo A, et al. Oxidative phosphorylation selectively orchestrates tissue macrophage homeostasis. *Immunity*. 2023;56(3):516–530.e519. doi:10.1016/j.immuni.2023.01.011
153. Guo Q, Kang H, Wang J, et al. Inhibition of ACLY leads to suppression of osteoclast differentiation and function via regulation of histone acetylation. *J Bone Mineral Res*. 2021;36(10):2065–2080. doi:10.1002/jbmr.4399
154. Meng L, Lu C, Wu B, et al. Taurine antagonizes macrophages M1 polarization by mitophagy-glycolysis switch blockage via dragging SAM-PP2Ac transmethylation. *Front Immunol*. 2021;12:648913. doi:10.3389/fimmu.2021.648913
155. Li Q, Song H, Li S, et al. Macrophage metabolism reprogramming EGCG-Cu coordination capsules delivered in polyzwitterionic hydrogel for burn wound healing and regeneration. *Bioactive Mater*. 2023;29:251–264. doi:10.1016/j.bioactmat.2023.07.011
156. Yeudall S, Upchurch CM, Seegren PV, et al. Macrophage acetyl-CoA carboxylase regulates acute inflammation through control of glucose and lipid metabolism. *Sci Adv*. 2022;8(47):eabq1984. doi:10.1126/sciadv.abq1984
157. Lauterbach MA, Hanke JE, Serefidou M, et al. Toll-like receptor signaling rewires macrophage metabolism and promotes histone acetylation via ATP-citrate lyase. *Immunity*. 2019;51(6):997–1011.e1017. doi:10.1016/j.immuni.2019.11.009
158. Li Y, He Y, Zheng Q, et al. Mitochondrial pyruvate carriers control airway basal progenitor cell function through glycolytic-epigenetic reprogramming. *Cell Stem Cell*. 2025;32(1):105–120.e106. doi:10.1016/j.stem.2024.09.015
159. Keating ST, Groh L, van der Heijden C, et al. The Set7 lysine methyltransferase regulates plasticity in oxidative phosphorylation necessary for trained immunity induced by β-glucan. *Cell Rep*. 2020;31(3):107548. doi:10.1016/j.celrep.2020.107548
160. Ferreira AV, Kostidis S, Groh LA, et al. Dimethyl itaconate induces long-term innate immune responses and confers protection against infection. *Cell Rep*. 2023;42(6):112658. doi:10.1016/j.celrep.2023.112658
161. Ding C, Shrestha R, Zhu X, et al. Inducing trained immunity in pro-metastatic macrophages to control tumor metastasis. *Nat Immunol*. 2023;24(2):239–254. doi:10.1038/s41590-022-01388-8
162. Feng YW, Wu C, Liang FY, et al. hUCMSCs mitigate LPS-induced trained immunity in ischemic stroke. *Front Immunol*. 2020;11:1746. doi:10.3389/fimmu.2020.01746
163. Saaoud F, Liu L, Xu K, et al. Aorta- and liver-generated TMAO enhances trained immunity for increased inflammation via ER stress/mitochondrial ROS/glycolysis pathways. *JCI Insight*. 2023;8(1). doi:10.1172/jci.insight.158183
164. Li X, Wang H, Yu X, et al. Maladaptive innate immune training of myelopoiesis links inflammatory comorbidities. *Cell*. 2022;185(10):1709–1727.e1718. doi:10.1016/j.cell.2022.03.043
165. Al B, Suen TK, Placek K, et al. Innate (learned) memory. *J Allergy Clin Immunol*. 2023;152(3):551–566. doi:10.1016/j.jaci.2023.06.014
166. Kalafati L, Hatzioannou A, Hajishengallis G, et al. The role of neutrophils in trained immunity. *Immunol Rev*. 2023;314(1):142–157. doi:10.1111/imr.13142
167. Bekkering S, Domínguez-Andrés J, Joosten LAB, et al. Trained immunity: reprogramming innate immunity in health and disease. *Ann Rev Immunol*. 2021;39:667–693. doi:10.1146/annurev-immunol-102119-073855
168. Ziogas A, Bruno M, van der Meel R, et al. Trained immunity: target for prophylaxis and therapy. *Cell Host Microbe*. 2023;31(11):1776–1791. doi:10.1016/j.chom.2023.10.015
169. Wang Y, Zhang S, Li H, et al. Small-molecule modulators of toll-like receptors. *Accounts Chem Res*. 2020;53(5):1046–1055. doi:10.1021/acs.accounts.9b00631
170. Li Y, Zhang L, Ren P, et al. Qing-Xue-Xiao-Zhi formula attenuates atherosclerosis by inhibiting macrophage lipid accumulation and inflammatory response via TLR4/MyD88/NF-κB pathway regulation. *Phytomedicine*. 2021;93:153812. doi:10.1016/j.phymed.2021.153812
171. Kang C, Li X, Liu P, et al. Tolerogenic dendritic cells and TLR4/IRAK4/NF-κB signaling pathway in allergic rhinitis. *Front Immunol*. 2023;14:1276512. doi:10.3389/fimmu.2023.1276512
172. Kalia N, Singh J, Kaur M. The role of dectin-1 in health and disease. *Immunobiology*. 2021;226(2):152071. doi:10.1016/j.imbio.2021.152071
173. Kunanopparat A, Dinh TTH, Ponpakdee P, et al. Complement receptor 3-dependent engagement by Candida glabrata β-glucan modulates dendritic cells to induce regulatory T-cell expansion. *Open Biol*. 2024;14(5):230315. doi:10.1098/rsob.230315
174. Jeyanathan M, Vaseghi-Shanjani M, Afkhami S, et al. Parenteral BCG vaccine induces lung-resident memory macrophages and trained immunity via the gut-lung axis. *Nat Immunol*. 2022;23(12):1687–1702. doi:10.1038/s41590-022-01354-4
175. Chen J, Gao L, Wu X, et al. BCG-induced trained immunity: history, mechanisms and potential applications. *J Transl Med*. 2023;21(1):106. doi:10.1186/s12967-023-03944-8
176. Liang J, Zhu F, Cheng K, et al. Outer membrane vesicle-based nanohybrids target tumor-associated macrophages to enhance trained immunity-related vaccine-generated antitumor activity. *Adv Mater*. 2023;35(46):e2306158. doi:10.1002/adma.202306158