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Macrophage metabolomics provides new insights into the metabolic markers and mechanisms of inflammation: review

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ABSTRACT

Macrophages are the core effector cells of the innate immune system. The dysregulation of amino acid, glucose, lipid, and energy metabolism in macrophages has a profound impact on inflammatory pathways. A comprehensive analysis of metabolites in macrophages can identify inflammatory metabolic biomarkers, elucidate inflammatory metabolic pathways, and provide a deep understanding of inflammation. Metabolomics technology, as a high-throughput detection method for analyzing small molecule metabolites in the body, can reveal the relationship of metabolic networks by detecting changes in the metabolites of macrophages. Therefore, this review summarizes the application of metabolomics in macrophages, comprehensively elaborates the metabolic network within macrophages, and aims to provide a new perspective for the discovery of potential inflammatory biomarkers and therapeutic targets.

1. Introduction

Metabolomics is a discipline that studies metabolic changes in biological systems by analyzing small-molecule metabolites in biological samples. These metabolites include, but are not limited to, amino acids, lipids, carbohydrates, hormones, and nucleotides. They are direct products of cellular metabolic activities and can reflect the physiological and pathological states of an organism[1]. Metabolomics is a new "omics" field that follows genomics, proteomics, and transcriptomics[2]. Genomes and proteomes exhibit cumulative and compensatory effects, so that even small changes can be amplified in metabolites. Therefore, the identification of metabolites is easier and more accurate to reflect the state of biological systems.

Inflammation is a complex biological process involving the activation of immune cells, the release of cytokines, and the reprogramming of metabolic pathways. During the inflammatory response, immune cells like macrophages undergo metabolic reprogramming to fulfill their energy and biosynthetic demands. This functional plasticity is dependent on specific changes in their metabolic programs. These metabolic changes not only support immune cell function but may further regulate the inflammatory process through the production of specific metabolites. Metabolomics perfectly meets the detection requirements for changes. It can conduct a detailed analysis of the metabolic changes in inflammation, reveal the metabolic mechanisms of inflammation, identify new inflammatory

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biomarkers, and provide new ideas for the diagnosis and treatment of inflammatory diseases. Cellular metabolomics can reveal the basic laws of life activities at the cellular level by studying the metabolites and their changes in cells. Macrophages are the frontline cells of the innate immune system, playing a crucial role in both the promotion and resolution of inflammation in its early stages. RAW264.7 and THP-1 are widely recognized as classical cell models in immunological research. Therefore, we summarize the application of metabolomics technology in the study of inflammatory mechanisms in RAW264.7 and THP-1 over the past 3 years, to provide new insights for elucidating the complex metabolic basis of inflammation, screening for inflammatory diagnostic markers, and identifying therapeutic targets.

2. Introduction to metabolomics

Metabolomics analysis techniques mainly utilize tools such as nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry (MS), which can conduct research and analysis of metabolites at 4 levels: targeted, fingerprinting, metabolic profiling, and metabolomics. Metabolomics is divided into targeted and untargeted approaches based on research objectives. Targeted metabolomics focuses on precise quantification of specific metabolites/classes, with common data acquisition modes including selected reaction monitoring (SRM)/multiple reaction monitoring (MRM) and parallel reaction monitoring (PRM). SRM is a technique based on triple quadrupole MS, which achieves high specificity and high sensitivity in quantitative analysis by monitoring specific pairs of precursor and product ions. In the first quadrupole, the preset precursor ions are selected, fragmented in the collision cell to produce product ions, and then detected in the second quadrupole. PRM is a derivative technique of SRM, based on high-resolution mass spectrometers (such as Q-orbitrap). After selecting the target precursor ions, all the fragment ions are subjected to full-scan detection. The quadrupole selects the target precursor ions, which are fragmented in the collision cell, and the high-resolution mass spectrometer detects all the fragment ions. Untargeted metabolomics is an unbiased method for detecting dynamic changes in small-molecule metabolites, with 2 main acquisition modes: data-dependent acquisition (DDA) and data-independent acquisition (DIA). Under DDA mode, the mass spectrometer selects the ions with the highest abundance for fragmentation and MS2 analysis based on their intensity in the MS1 scan. This mode prioritizes the detection of high-abundance metabolites but potentially overlooks low-abundance ones due to weaker signals. In DIA mode, the mass spectrometer fragments all precursor ions within divided scanning windows and acquires full product ion spectra. Independent of precursor ion intensity, this mode comprehensively collects unbiased, complete fragment information without omission. The basic principles of targeted and untargeted metabolomics are shown in Fig. 1.

There are limitations in targeted or untargeted metabolomics. Targeted metabolomics can only analyze pre-defined specific metabolites or pathways (such as amino acids or short-chain fatty acids in specific pathways), and cannot detect new metabolites or unknown pathways. Meanwhile, the number of metabolites that can be quantitatively analyzed is limited, making it difficult to comprehensively cover complex metabolic networks. The coexistence of high and low abundance metabolites is easily disturbed by ion suppression effects. Non-targeted metabolomics detects all metabolites comprehensively, but lacks isotope internal calibration, and the results only show the relative abundance changes of metabolites. High-throughput analysis is prone

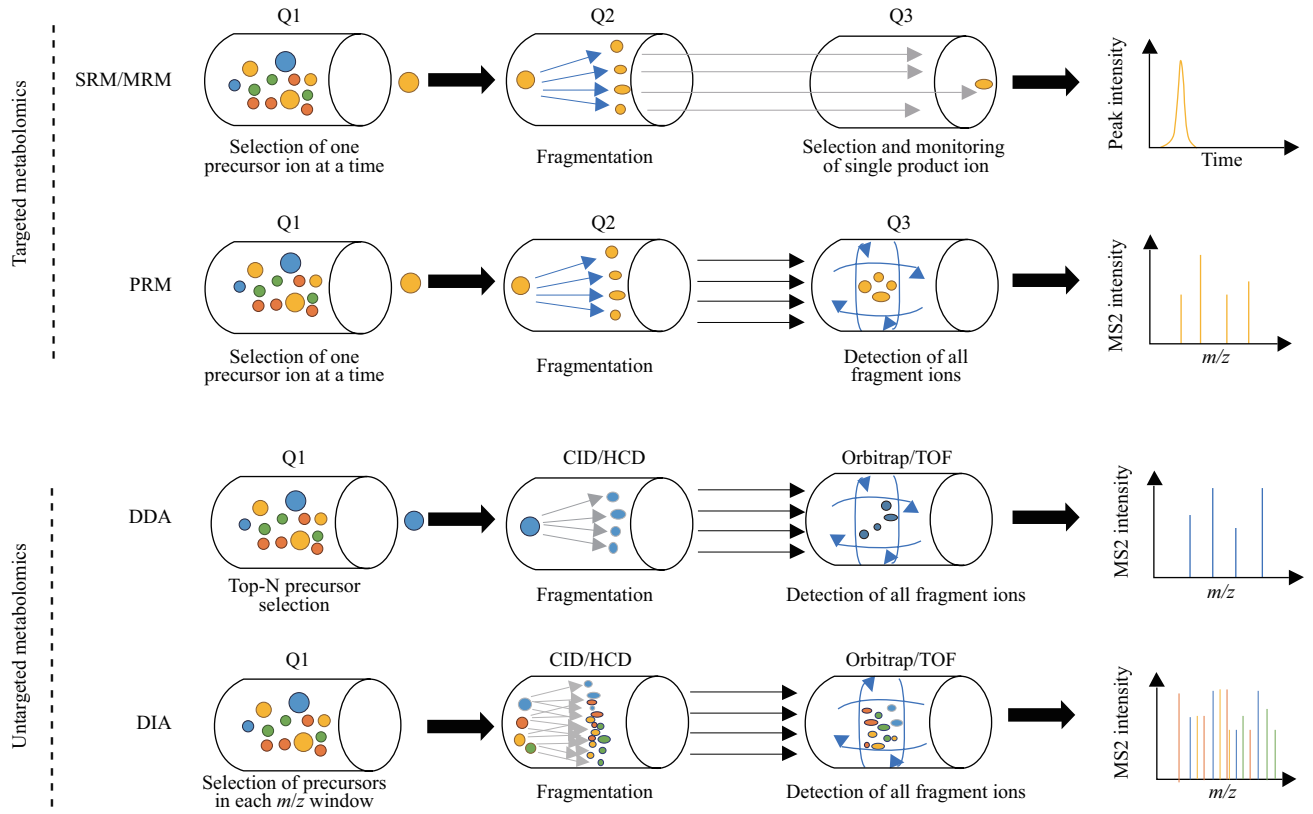

Fig. 1 Schematic diagram of the basic principles of targeted and untargeted metabolomics. CID, collision-induced dissociation; HCD, higher-energy collisional dissociation; TOF, time-of-flight. Q1 refer to the first quadrupole mass analyzer; Q2 refers to the collision cell; Q3 refer to the third quadrupole mass analyzer.

to generating a large amount of noise signals, resulting in false-positive differential metabolites. The incomplete coverage of the database further increases the risk of erroneous annotations. Untargeted metabolomics is more suitable for exploratory research, such as discovering new biomarkers or understanding metabolic changes under disease states. In contrast, targeted metabolomics is better suited for validating metabolites identified in untargeted metabolomics or for in-depth research on known metabolic pathways.

In the analysis of metabolomics data, principal component analysis (PCA), partial least squares discriminant analysis (PLS-DA), and orthogonal partial least squares discriminant analysis (OPLS-DA) are 3 commonly used multivariate statistical methods[3]. Before conducting these analyses, metabolomics data need to be preprocessed, including steps such as noise reduction, baseline correction, peak alignment, binning, normalization, and data scaling, to ensure data quality and the accuracy of the analysis results.

3. Applications of metabolomics in macrophage inflammation

The phenotypic plasticity of macrophages is the cornerstone of their diversified immune functions, and metabolic reprogramming constitutes the core molecular mechanism of this plasticity. Metabolites not only serve as sources of energy and for biosynthesis, but also act as key signaling molecules that regulate gene expression and signaling pathways. Metabolomics reveals the metabolite characteristics of different phenotypes of macrophages, providing a key basis for understanding the regulatory mechanism of phenotypic plasticity and immune function, and facilitating the discovery of disease targets and the development of therapeutic strategies.

3.1 Amino acid metabolism

In the inflammatory response, amino acid metabolism can provide a large amount of energy and biosynthetic precursors necessary for the activation and proliferation of immune cells. However, the expression of amino acids varies under different stimulation conditions and in different cell lines. These expression differences directly influence immunomodulation. Metabolomics analysis reveals that after lipopolysaccharide (LPS) stimulation of RAW264.7 macrophages, the levels of arginine, glutamine, tryptophan, glutamate, glycine, phenylalanine, leucine, and proline all increase[4]. In THP-1 cells, the metabolism of arginine, alanine, aspartate, and glutamate is significantly altered after LPS stimulation. Details are provided in Table 1. The elevation of multiple amino acid levels in macrophages after LPS stimulation reflects their metabolic reprogramming to meet the energy and biosynthetic demands of the inflammatory response. This phenomenon not only supports the immune functions of macrophages but also reveals the close association between amino acid metabolism and immunity, providing important clues for understanding the mechanisms of inflammatory diseases and developing therapeutic strategies.

3.1.1 Arginine metabolism

After LPS stimulation, arginine levels significantly increased in THP-1 and RAW264.7 cells, indicating that arginine plays a crucial role in inflammatory responses[5-6]. Arginine is involved in the regulation of a variety of biological functions, including cell proliferation, cell signaling, immune response, neurotransmission, and the generation of other amino acids[7]. The metabolic pathways of arginine primarily follow 2 directions: one pathway breaks down arginine into ornithine and urea by arginase (ARG); the other is the conversion of arginine into citrulline and nitric oxide (NO) catalyzed by nitric oxide synthase (NOS)[8]. Under normal circumstances, these 2 metabolic pathways maintain a mutually restraining equilibrium. However, during chronic inflammatory processes, this balance may be disrupted, leading to alterations in the activities of enzymes involved in the arginine metabolic pathways. The arginine metabolic pathway is involved in the activation and polarization of macrophages. The promotion of inducible nitric oxide synthase (iNOS) activity leads to the production of NO from arginine. NO is an important signaling molecule that has antibacterial properties, regulates inflammatory responses, and enhances the functions of immune cells[9]. In the innate immune response, ARG1 can participate in the regulation of inflammatory responses and immune tolerance through the arginine metabolic pathway[10]. ARG1 interacts with other immune regulatory molecules, including signal transducer and activator of transcription 3 (STAT3), interleukin (IL)-4, and IL-10, forming a complex network that regulates immune responses. When cytokines like IL-4 or IL-10 activate the JAK/STAT pathway, STAT3 is phosphorylated, translocated to the nucleus, and binds to the promoter region of the *ARG1* gene to promote its transcription. This regulatory mechanism is particularly important in the M2-type macrophages, and ARG1 is also one of the signature enzymes of M2-type macrophages[11-12]. Arginine can enhance monocyte migration and the production of pro-inflammatory cytokines in peripheral blood during the early stages of inflammation. In the later stages of inflammation, arginine can also inhibit the activity of immune cells and regulate the immune state. Mechanistic studies have found that arginine can modulate the nuclear factor kappa-B (NF-κB) and JAK/STAT signaling pathways involved in inflammatory responses[13-14]. Additionally, arginine can also activate the mammalian target of rapamycin (mTOR) signaling pathway, which is involved in proteinlipid and nucleotide synthesis[15].

3.1.2 Glutamine metabolism

Glutamine, the most abundant free amino acid in the human body, serves as a crucial substrate for enterocytes and immune cells. It is crucial for the proliferation and activation of macrophages and also serves as an important amino acid involved in inflammatory responses. Glutamine is synthesized from glutamate and ammonia by the catalytic action of glutamine synthetase (GS). Glutamine is broken down into glutamate and ammonia by the action of glutaminase (GLS), and glutamate is further metabolized into α-ketoglutarate (α-KG), which enters the tricarboxylic acid (TCA) cycle to produce energy and metabolic intermediates. In amino acid metabolism, increased glutamine metabolism is another characteristic of M2-type macrophages, which is different from M1-type macrophages[16]. Glutamine plays a crucial role in M2-type macrophages, with 1/3 of the carbon in the TCA cycle metabolites of M2-type macrophages originating from glutamine[17]. The α-KG produced from glutamine catabolism can promote the epigenetic activation of M2-type macrophage genes[18-19]. Under inflammatory conditions, glutamine can inhibit oxidative stress and cytokine production by downregulating the NF-κB and STAT signaling pathways. When combined with arginine, it can

Table 1
Summary of metabolomics related to amino acid metabolism in inflammatory cells.

Cell type	Model	Experiment	Methods	Major amino acid metabolites	References
RAW264.7	LPS		Untargeted	Arginine	[5]
RAW264.7	LPS	Patchouli	Untargeted	Arginine, *L*-leucine, cholesterol, fructose, tryptophan, and proline	[34]
RAW264.7	LPS	Terpinen-4-ol	Untargeted	Glycine, serine, glutamine, *L*-threonine, pyridoxine, *DL*-homoserine	[19]
RAW264.7	*Aspergillus medius* polysaccharide		Untargeted	Glutamate, arachidonic acid (AA)	[55]
RAW264.7	Retinol		Untargeted	Arginine, proline	[56]
RAW264.7	LPS	(*R*)-Salbutamol	Untargeted	Phenylalanine	[57]
RAW264.7	LPS	Vitamin D_3	Untargeted	Argininosuccinic acid, *L*-alanine	[58]
RAW264.7	LPS	Catechin	Untargeted	*L*-Methionine-*S*-oxide, *S*-glutathionyl-*L*-cysteine, γ-glutamylcysteine	[59]
RAW264.7	LPS	Pentapeptide (SFRWQ)	Untargeted	Glutathione (GSH), glutathione disulfide (GSSG), γ-glutamylcysteine, prostaglandin D2 (PGD2), prostaglandin E2 (PGE2), prostaglandin H2 (PGH2)	[60]
RAW264.7	Perfluorooctanoic acid		Untargeted	Glutamine	[61]
RAW264.7	LPS	Chuanwang xiaoyan capsules	Untargeted	Glutamate, glutathione, arginine, proline, argininosuccinic acid	[62]
RAW264.7	LPS	Selenium-enriched green tea	Untargeted	Valine, phenylalanine, pyridoxal 5'-phosphate	[63]
RAW264.7	LPS	Yuhuanglian	Untargeted	Arginine, proline, aspartate, glutamate, S1P	[64]
RAW264.7	LPS	Graphene oxide quantum dots (GOQDs)	Untargeted	Phosphatidylcholine (PC), monoolein, elaidic acid, PGE2, 18-hydroxyeicosapentaenoic acid (18-HEPE), prostaglandin B1, ACh	[65]
RAW264.7	LPS	Homeobox containing 1-overexpressed	Untargeted	Glutamine	[4]
RAW264.7	LPS	Mahuang Fuzi decoction	Untargeted	Arginine, proline	[66]
RAW264.7	LPS	3-Cinnamoyltribuloside	Untargeted	Phenylalanine, alanine, lysine, homoserine, sarcosine, glycine, histidine, glutathione	[67]
THP-1	Nicotine		Untargeted	*L*-Glutamate, proline, citrulline, arginine, ornithine	[68]
THP-1	High glucose + high fat		Untargeted	*L*-Arginine, *L*-glutamate, proline	[69]
THP-1	Spike protein of SARS-CoV-2	Antcin A	Untargeted	Sarcosine, glycine, ethanolamine, phosphoenolpyruvic acid	[70]
THP-1	5% CO_2 + LPS	10% CO_2 + LPS	Untargeted	Proline	[71]
THP-1	5-Fluorouracil (5-FU)	NaAc	Untargeted	Glutamate, sphingosine	[72]
THP-1	AGEs	NaB	Untargeted	*L*-Glutamic acid, arginine, alanine, aspartate, PC	[73]
THP-1	Phloretin		Untargeted	*N*-Methylglutamic acid, lglutamic acid, *N*-acetyl-L-aspartic acid, *L*-asparagine, *D*-aspartic acid	[74]
THP-1	High glucose + high fat		Untargeted	*L*-Arginine, *L*-glutamate, arginine, proline, glycerophospholipid	[69]
THP-1	Chlorinated polycyclic aromatic hydrocarbons		Untargeted	Glutamate, aspartate	[75]
THP-1	Oxidized low-density lipoprotein (ox-LDL)		Untargeted	Glutamic acid, glycine	[76]

regulate p38MAPK to inhibit the production of tumor necrosis factor (TNF)-α and other pro-inflammatory cytokines, alleviating inflammatory responses[20-22]. Supplementing with glutamine can promote the proliferation of epithelial cells by activating the mTOR signaling pathway[23-24]. Glutamine can regulate intracellular signaling pathways through its metabolic products, inhibiting the production of inflammatory cytokines and chemokines, and alleviating intestinal inflammatory responses[25]. Modulating glutamine metabolism can mitigate inflammatory responses and offer a novel strategy for anti-inflammatory therapies.

3.1.3 Tryptophan metabolism

Tryptophan is an essential amino acid for the human body and plays an important role in biological transformation and signal transduction. Tryptophan metabolism is divided into 3 main pathways: the kynurenine (Kyn) pathway, the 5-hydroxytryptamine (5-HT) pathway, and the indole pathway. By regulating different pathways of tryptophan metabolism, various physiological functions can be modulated, including inflammation, metabolism, immune response, and neural function[26]. Tryptophan can be converted into indole substances by the intestinal microbiota. These indole compounds

(including indole, indole-3-acetic acid, and indole-3-propionic acid) can significantly upregulate the expression of the aryl hydrocarbon receptor (AhR), inhibit the activation of the NF-κB signaling pathway and the formation of the NLR family, pyrin domain containing 3 (NLRP3) inflammasome, and reduce the release of inflammatory cytokines, thereby alleviating the inflammatory response[27-29]. Kyn is one of the main metabolites of tryptophan metabolism and has immunomodulatory effects. Kyn further activates the AhR, leading to the upregulation of suppressor of cytokine signaling 3 (SOCS3), which inhibits the JAK-STAT1 signaling pathway, reducing the secretion of T cell chemokines C-X-C motif chemokine (CXCL) 9 and CXCL10[30]. These chemokines are crucial for recruiting T cells to the lungs. In addition, tryptophan is metabolized into 5-HT in the serotonin pathway. 5-HT activates Jak1/STAT3/ERK1/2 and NF-κB signaling pathway, participating in the inflammatory response[31]. The depletion of tryptophan can activate the general control non-derepressible 2 (GCN2) pathway and inhibit the mTOR pathway, and also affects the protein kinase C signaling pathway. These changes lead to autophagy, reduced function of T cells, decreased anti-inflammatory capacity, and exacerbation of inflammatory responses[32]. It has been reported that in macrophages infected with mycobacterium tuberculosis (H37Rv), the expression of genes related to tryptophan metabolism has significantly changed, with an increase in the expression of tryptophan 2,3-dioxygenase 2 (TDO2), which may in turn affect the immune response and inflammatory processes of the host cells[33]. Therefore, targeting tryptophan metabolism may be a potential strategy to treat inflammation.

3.1.4 Leucine metabolism

Leucine is also significantly upregulated in LPS-stimulated immune cells, which can modulate the polarization state of macrophages to influence inflammatory responses[34]. Studies have shown that leucine-induced macrophage polarization through the mechanistic target of rapamycin complex 1 (mTORC1)/liver X receptor α (LXRα) pathway, which synergistically enhanced the expression of the IL-4-induced M2 marker Arg1 and subsequent M2 polarization[35]. Leucine binds to Sestrin2, a negative regulator of mTORC1 activity, promoting mTORC1 activation and thereby promoting protein synthesis in the liver and other tissues[36]. Hypoxia-inducible factor-1α (HIF-1α), a downstream effector of the mTOR signaling pathway with multiple biological activities, enhances autophagy in macrophages to clear pathogens, regulates immune cells and cytokines, and participates in immune regulation[37]. In macrophages, HIF-1α can promote polarization towards the M1-type phenotype, increase the production of pro-inflammatory cytokines, and disrupt epithelial autophagy, exerting pro-inflammatory effects[38]. However, some studies have indicated that spermidine can induce AMP-activated protein kinase through mitochondrial reactive oxygen species (ROS), upregulate HIF-1α and autophagy levels under normoxic conditions, and shift macrophages towards the M2 phenotype[39]. Therefore, the regulatory role of HIF-1α in macrophages still requires further investigation. Leucine regulates inflammatory responses through various mechanisms, including promoting macrophage polarization and modulating inflammation-related signaling pathways. These actions provide new therapeutic targets for inflammation-related diseases.

3.1.5 Glycine metabolism

Glycine can be converted from threonine *via* threonine dehydrogenase or serine *via* serine hydroxymethyltransferase (SHMT). It is a novel natural regulator with anti-inflammatory, immunomodulatory, and cell-protective effects, including significant anti-inflammatory properties and the ability to inhibit inflammatory responses through multiple mechanisms[40]. Glycine is closely related to macrophage polarization, which can reduce cytokine levels and increase the proportion of M2/M1 polarized macrophages[41]. Studies have shown that glycine can reduce the levels of pro-inflammatory cytokines by regulating the NF-κB signaling pathway and downregulating the phosphorylation of ERK1/2, c-Jun amino-terminal kinase (JNK), and p38MAPK[42-43]. Glycine also promotes Akt activation by suppressing phosphatase and tensin homolog (PTEN), inhibiting NF-κB and HIF-1α signaling pathway[43]. In addition, glycine exhibits antioxidant properties by up-regulating the Nrf-2/HO-1 signaling pathway, which reduces ROS production and inhibits NLRP3 in M1-type macrophages[44-45].

3.1.6 Phenylalanine metabolism

Phenylalanine is an essential amino acid belonging to the aromatic group. The relationship between phenylalanine and inflammation has gradually been revealed in recent years, especially in the role of diabetic wound healing, chronic inflammatory diseases, and immune responses[46]. Phenylalanine supplementation promotes valine-succinyl-CoA metabolism, promoting oxidative phosphorylation pathway (OXPHOS), reducing Caspase-1 activation in pro-inflammatory macrophages, and reducing IL-1β production[47]. Phenylalanine also inhibits ROS-induced oxidative damage by up-regulating nuclear factor erythroid 2-related factor 2 (Nrf2) expression and down-regulating kelch-like ECH-associated protein 1 (Keap1) expression[48]. In addition, phenylalanine metabolites are also involved in the regulation of inflammation. For example, phenylpyruvic acid is one of the intermediates of phenylalanine metabolism, and phenylpyruvic acid can increase the expression level of NLRP3 and maintain the polarization of pro-inflammatory macrophages[46].

3.1.7 Proline metabolism

Proline is also a key modulator of inflammatory responses, functioning as both a pro-inflammatory and anti-inflammatory factor depending on the specific cell type and inflammatory context. Proline metabolism produces electrons to produce ROS and trigger a variety of downstream effects, including cell cycle arrest, autophagy, and apoptosis. These electrons can also enter the electron transport chain to produce adenosine triphosphate (ATP), which is essential for survival under nutritional stress[49]. Proline can be metabolized to glutamic acid, which is subsequently deaminated to α-ketoglutaric acid, entering the TCA cycle[50]. Additionally, proline and proline polypeptide complexes activate the NF-κB or MAPK signaling pathways, promoting the production of inflammatory factors[51-52]. In addition, proline, as an important immunomodulatory substance, is involved in the regulation of various immune responses. It promotes the maturation and proliferation of immune cells, regulates T cell differentiation, modulates the intracellular redox environment and protects mammalian cells against oxidative

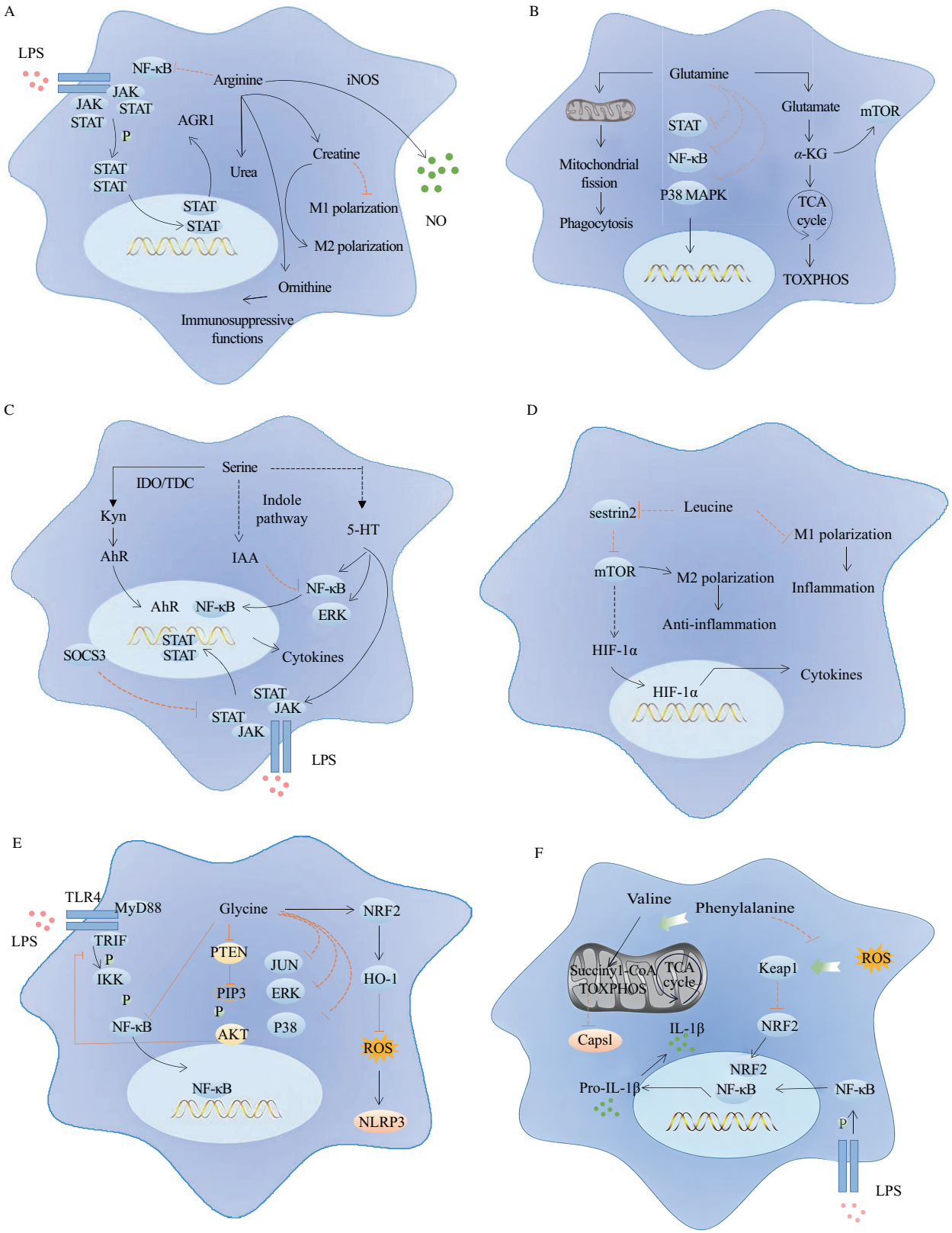

Fig. 2 Mechanism diagram of the amino acid metabolism. (A-F) Arginine metabolism, glutamine metabolism, serine metabolism, leucine metabolism, glycine metabolism, and phenylalanine metabolism, respectively.

stress[53-54]. Further research on the immunomodulatory effects of proline will help to develop new immunomodulatory strategies for the treatment of immune-related diseases. The mechanism diagram is shown in Fig. 2.

In summary, amino acid metabolism plays a multifaceted role in inflammatory responses, not only supporting the function of immune cells but also directly participating in the regulation of inflammatory processes through the production of specific metabolites. By modulating the availability of specific amino acids or targeting different amino acid metabolic pathways, it is possible to modulate immune responses, reduce inflammation, and potentially improve disease outcomes. These findings provide new perspectives and potential targets for the diagnosis and treatment of inflammatory diseases.

3.2 Glucose metabolism

Glucose metabolism is the primary means of energy synthesis in cells and is essential for maintaining the life activities of organisms. Intracellular glucose metabolism includes glycolysis, TCA cycle, OXPHOS, pentose phosphate pathway (PPP), glycogen synthesis and decomposition, gluconeogenesis, and many other pathways. Macrophages can meet their energy and biosynthesis needs through different glucose metabolism pathways depending on the activation state and environmental conditions. Metabolomics analysis reveals that glucose-6-phosphate (G6P), pyruvate (PYR), lactic acid (LAC), glyceraldehyde 3-phosphate (G3P), 3-phosphoglyceric acid (3-PGA), phosphoenolpyruvate (PEP), and other metabolites in the glycolysis stage are changed under inflammatory conditions. Metabolomics analysis also reveals that the levels of aconitic acid (ACON), citric acid (CIT), 2-oxoglutaric acid (2-OG), succinic acid (SUC), fumaric acid (FUM), and malic acid (MAL) are significantly changed in the TCA cycle. Inflammatory conditions also elevate metabolites in the PPP pathway, including glucose-6-phosphate dehydrogenase (G6PD) and reduced coenzyme II (NADPH). These changes involve the regulation of various metabolites and enzymes, reflecting the metabolic adaptability of macrophages in the inflammatory response. Details are provided in Table 2.

3.2.1 Glycolytic pathway

Glycolysis is an important metabolic pathway in living organisms that breaks down glucose into PYR, producing energy in the process[77]. Glycolysis is involved in the polarization of macrophages and is a key metabolic feature of M1-type macrophages. Under pro-inflammatory signals (such as LPS, type II interferon (IFN)-γ) stimulation, macrophages rapidly generate ATP by enhancing aerobic glycolysis (the Warburg effect), meeting their high energy demands, but impairing the TCA cycle[78-79]. In contrast, M2-type macrophages produce ATP mainly through the TCA cycle coupled oxidative phosphorylation[80]. Three key rate-limiting enzymes in glycolysis include hexokinase (HK), phosphofructo-kinase (PFK)-1, and pyruvate kinase (PK). The first key enzyme, HK1, converts glucose into G6P, initiating glycolysis and energy production. Inflammatory factors upregulate the mRNA level of *HK1*, and glycolysis involving HK1 promotes the activation of cellular inflammatory responses[81-82]. The N-terminus of HK1 contains the mitochondrial binding domain (MBD). Mitochondrial-bound HK1 catalyzes G6P metabolism *via* glycolysis. However, upon dissociation from mitochondria, G6P is redirected to the PPP, promoting inflammatory factor production[83]. During the polarization of macrophages, PI3K can regulate MYC proto-oncogene (c-MYC), which can then increase lactic acid (LAC) production by regulating the activity of lactate dehydrogenase (LDHA)[84]. Lactate inhibits the expression of interferon regulatory factor 4 (IRF4), and the elimination of IRF4 can enhance M1 polarization and increase the production of pro-inflammatory cytokines[85-86]. LPS also enhances glycolysis by activating the PI3K/Akt and HIF-1α pathway, which promotes the expression of glycolytic enzymes such as HK and

Table 2
Summary of metabolomics related to glucose metabolism in inflammatory cells.

Cell type	Model	Experiment	Methods	Sugar-related metabolites	References
RAW264.7	LPS	Terpinen-4-ol	Untargeted	*α*-KG	[19]
RAW264.7	LPS	LPS + adrenomedullin (ADM)	Targeted	F1,6BP, 3-phosphoglycerate, PYR, oxaloacetic acid, MAL, FUM, *α*-KG, LAC	[78]
RAW264.7	Retinol			Pyruvic acid, glutathione, argininesuccinic acid, MAL, F6P	[56]
RAW264.7	LPS	Vitamin D_3	Untargeted	Linoleic acid, CIT, MAL	[58]
RAW264.7	LPS	Chuanwang Xiaoyan Capsules	Untargeted	Phosphorylcholine	[62]
RAW264.7	LPS			*L*-Prolinamide, ITA, SUC, calonectrin, *D*-glucopyranoside, propionylcarnitine, MAL, *L*-isoleucinamide, phosphodimethylethanolamine, phosphorylcholine, phosphocreatine, argininosuccinic acid, glycero phosphoglycerol, guanosine monophosphate, oleoyl-CoA, flavin adenine dinucleotide, adenosine, diphosphate	[62]
RAW264.7	LPS	*Sargentodoxa cuneata* and *Patrinia villosa* extract	Untargeted	UDP-*α*-*D*-glucose, pyruvic acid, cytarabine, guanosine, glutathione	[109]
RAW264.7	LPS	Silica	Untargeted	Succinate, itaconate, glutamate, glutamine	[110]
THP-1	MSU	MSU + IL-17	Untargeted	LAC, glyceraldehyde-3-phosphate, CIT, succinate,	[111]
THP-1	Phloretin/Phlorizin			PC, phosphatidylglycerol (PG), phatidylethanolamines, *sn*-glycero-3-phosphocholine, glycerophospholipid, sphingolipid	[74]
THP-1	Hepatitis B virus (HBV)		Targeted	Citrate, PYR dehydrogenase complex hyperacetylation	[112]
THP-1	LPS	WS2 nanosheets	Untargeted	PYR, lactate	[114]
THP-1	Zinc oxide (ZnO) nanoparticles (NPs)		Untargeted	Acetyl CoA, citrate, malate, fumarate, ribose-5-phosphate	[115]

phosphofructokinase[87]. PFK-1, the second rate-limiting enzyme in glycolysis, phosphorylates F6P to fructose-1,6-bisphosphate (F1,6BP), serving as a key control point for regulating glycolytic flux. LPS enhances the activity of PFK-1, leading to increased glycolysis rates and LAC production. Downregulating PFK-1 expression by inhibiting fructose-2,6-bisphosphatase 3 (PFKFB3) reverses the LPS-induced inflammatory effects, reducing IL-1β secretion[88]. PFK-2 catalyzes the synthesis and degradation of fructose-2,6-diphosphate (F2,6-BP), which is the activator of PFK-1 and therefore controls the rate of glycolysis[89]. Inhibition of PFKFB3 leads to reduced activation of NF-κB, which inhibits the expression of adhesion molecules, pro-inflammatory cytokines, and chemokines[90]. PK is the third rate-limiting enzyme in glycolysis, catalyzing the production of PYR. The expression of PKM2, an isoenzyme of PK, is significantly increased in LPS-activated macrophages and promotes LAC production and regulates cellular inflammation. LAC then increases nuclear translocation of PKM2 *via* a feedback loop, thereby inhibiting glycolysis[91]. In addition, PK is catalyzed by pyruvate de-hydrogenase complex (PDC) to convert acetyl-CoA to supply the TCA cycle. CIT from the TCA cycle is exported to the cytoplasm *via* CIT/isocitric acid transporters (CIC). In the cytoplasm, CIT is converted to acetyl-CoA by ATP-citrate lyase (ACLY), and acetyl-CoA is converted to malonyl-CoA by acetyl-CoA carboxylase (ACC) in the cytoplasm. Malonyl-CoA can induce malonylation of GAPDH in M1-type macrophages and enhance its glycolysis activity[92]. The mechanism diagram is shown in Fig. 3.

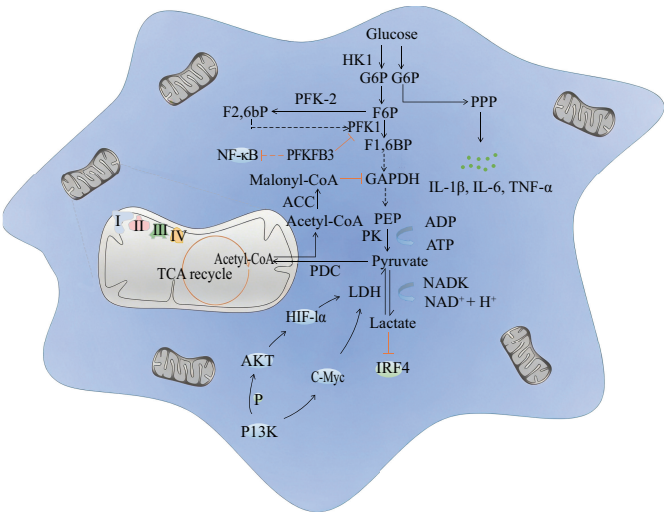

Fig. 3 Mechanism diagram of the process of the glycolytic pathway and associated inflammatory effects.

3.2.2 TCA cycle pathway and oxidative phosphorylation pathway

The TCA cycle is the core of cellular energy metabolism, linking carbohydrate, lipid, and protein metabolism. During inflammatory responses, metabolic reprogramming in immune cells (such as macrophages and dendritic cells) induces the accumulation and release of TCA cycle intermediates. These metabolites not only participate in energy metabolism but also act as signaling molecules to regulate immune and inflammatory responses. As the core of energy metabolism, the TCA cycle orchestrates intracellular metabolic regulation and initiates downstream signaling cascades. Metabolomics analysis reveals that various metabolites of the TCA cycle accumulate in large quantities during the inflammatory process, including CIT, SUC, isocitric acid, FUM, *α*-KG, MAL, etc.

In M1-type macrophages, the TCA cycle is repeatedly interrupted, resulting in the accumulation of intermediate metabolic products. The inhibition of isocitrate dehydrogenase (IDH) activity leads to the accumulation of citrate and its downstream metabolites (such as ACON), which is the typical metabolism in M1-type macrophage[93]. The NADPH produced by CIT generates ROS and NO under the action of NADPH oxidase and iNOS, respectively. The increase in NO level inhibits IDH activity and further promotes the accumulation of CIT and aconitonic acid downstream[94]. In LPS-stimulated macrophages, aconitate decarboxylase 1 (ACOD1) is rapidly induced to catalyze ACON decarboxylation to produce high concentrations of itaconic acid (ITA). ITA can also activate NRF2, increase the level of activated transcription factor 3 (ATF3), inhibit inhibitor of kappa B (IκB) activity, and play an anti-inflammatory role[95]. The accumulation of ITA regulates cellular metabolism by inhibiting succinate dehydrogenase (SDH) and inhibiting SDH-mediated reverse electron transport, thereby reducing mitochondrial ROS production[96-97]. SUC, as an intermediate metabolite of the TCA cycle, significantly accumulates after LPS stimulation, promotes the production of IL-1β, and drives inflammatory signals by inducing the stabilization of HIF-1α[98]. FUM accumulation is associated with inflammatory signaling and cancer development[99]. FUM is also a key metabolite of the TCA cycle and is increased during the M1-type macrophages. FUM accumulation can lead to the release of mtDNA or mtRNA, and the released mtRNA and mtDNA activate the RIG-I/MDA5-MAV signaling pathways, respectively, which trigger the transcription of IFN and participate in the inflammatory response[100].

M2-type macrophages produce energy primarily through the OXPHOS pathway and a complete TCA cycle[80]. This metabolism allows M2-type macrophages to efficiently use glucose and fatty acids to produce ATP to support their function. *α*-KG produced by glutamine metabolism can maintain the expression of M2-type phenotype genes and promote the activation of M2-type macrophages[101]. The mechanism study found that *α*-KG inhibited STAT3/NF-κB signaling to promote M2-type macrophage polarization, and inhibited HIF-1α signaling pathway and IL-1β production[102]. The anti-inflammatory metabolite ITA produced by M1-type macrophages also regulates the process of M2 polarization, and ITA can inhibit M2 polarization *via* inhibition of the JAK1/STAT6 signaling pathway downstream of IL-4[103]. This metabolic reprogramming highlights the potential of ITA as a therapeutic target for inflammatory diseases. Meanwhile, IL-10 secreted during M2-type macrophages can inhibit glucose uptake and glycolysis in M1-type macrophages and increase their OXPHOS[104]. During the M1/M2-type macrophages, the mutual regulation of glucose metabolism and its metabolites plays a key role in the function and polarization of macrophages. This metabolic regulation mechanism not only affects inflammation responses, but also plays an important role in maintaining body homeostasis. The mechanism diagram is shown in Fig. 4.

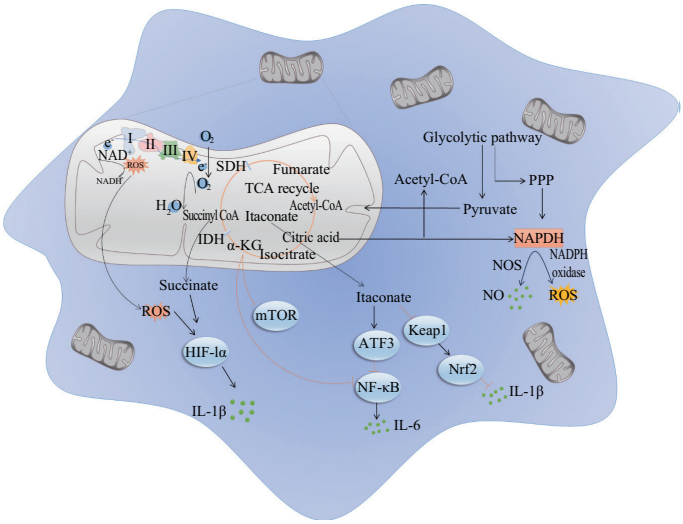

Fig. 4 Mechanism diagram of the process of the TCA cycle and associated inflammatory effects.

3.2.3 PPP

The PPP is a branch of glucose metabolism. Under LPS stimulation, PPP metabolism is enhanced, and the intermediates generated by PPP can enter the TCA cycle to generate energy. NADPH, the intermediate metabolite of PPP, serves as a hydrogen donor in the biosynthesis of fatty acids, cholesterol, steroid hormones, nucleotides and lipids, and also acts as a coenzyme for glutathione reductase[105]. M1-type macrophages stimulated by LPS rely on NADPH to produce ROS during respiratory bursts to play a bactericidal role[106]. The high expression of G6PD, a key enzyme of the PPP, can activate the downstream MAPKs and NF-κB signaling pathways, cause intracellular oxidative stress and pro-inflammatory cytokine expression, and induce macrophages to undergo M1-type polarization[107-108].

In LPS-treated cells, M1 macrophages rely on glycolysis and the PPP, while M2 macrophages utilize OXPHOS and the TCA cycle. It may be due to the heterogeneity of macrophages, polarization stimulation, and selection *in vitro* culture (primary or cell lines from different species, tissues, or progenitors) that may result in different biological and metabolic characteristics. These metabolites are not only involved in energy metabolism but also act as signaling molecules to regulate the activation of immune cells and the production of inflammatory mediators. The relationship between glucose metabolism and inflammation is multifaceted, involving immune response, metabolic pathways, and related inflammatory signaling pathways. These findings provide a theoretical basis for understanding the role of glucose in inflammatory diseases and provide potential targets for developing therapeutic strategies.

3.3 Lipid metabolism

Under normal physiological conditions, lipoprotein expression remains stable. However, in an inflammatory environment, lipoproteins may exhibit either upregulated or downregulated expression, accompanied by structural modifications or subcellular localization changes that are tightly linked to the regulation of inflammatory responses. Metabolomics analysis reveals that cholesterol, peroxisome proliferator-activated receptor gamma (PPARγ), free fatty acids (FFAs), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), prostaglandin E2 (PGE2), arachidonic acid (AA), 20-hydroxyeicosatetraenoic acid (20-HETE), sphingolipids, sphingosine, phosphocholine, sphingomyelin, and phosphatidylinositol (PI) are all significantly altered during inflammation. Details are provided in Table 3. Studying these changes and their mechanisms contributes to a deeper understanding of the pathophysiological processes of inflammation and provides a theoretical basis for developing anti-inflammatory treatment strategies.

3.3.1 Fatty acid metabolism

Fatty acid metabolism is an important form of cellular lipid metabolism, and it is also one of the energy sources of cells. First, fatty acids are catalyzed by Acyl-CoA synthetase to Acyl-CoA, which then enters the mitochondrial matrix and undergoes *β*-oxidation to produce Acetyl-CoA, reduced flavin adenine dinucleotide ($FADH_2$), and NADH. Acetyl-CoA enters the TCA cycle and is further oxidized and decomposed to generate a large amount of energy. In M1-type macrophages, TCA cycle disruption leads to the accumulation of excessive fatty acids, which are stored as triacylglycerols and cholesterol esters in lipid droplets[116]. The triglyceride (TAG) in the lipid droplet can be broken down into glycerol and FFAs by TAG lipase (ATGL) during the lipolysis process. Disturbances in lipid metabolism induce inflammation by affecting the M1/M2 polarization of macrophages[117-118]. In M1-type macrophages, LPS stimulation upregulates the fatty acid synthesis pathway, primarily due to increased expression of the fatty acid transporter CD36. This enhances fatty acid uptake, promotes TAG synthesis, and reduces catabolism, ultimately leading to cellular lipid accumulation and exacerbation of the local inflammatory response[119-120]. It has been reported that PPARγ is highly expressed in LPS-stimulated macrophages, regulating the expression of CD36 by binding to the response elements appearing in the proximal region of the CD36 promoter, promoting the process of lipid uptake, forming a positive feedback, and promoting the polarization towards M2-type macrophages[121-122]. In addition, PPARα can antagonize NF-κB and activator protein-1 (AP-1), negatively regulating proinflammatory cytokine gene expression levels[123]. PPAR has been identified as a key regulator of inflammation and fatty acid oxidation, regulated by the PI3K/AKT/mTOR signaling pathway[9]. During lipid metabolism, AA is released from cell membrane phospholipids with the action of phospholipase A2 (PLA2), followed by the production of prostaglandin H2 (PGH2) with the action of cyclooxygenase (COX). PGH2 is further transformed into PGE2 by different prostaglandin synthetases. PGE2 is an important inflammatory mediator that regulates inflammation by activating EP receptors[124]. Raptor (a key component of mTORC1) regulates prostaglandins synthesized by COX-2, which promotes the production of beige fat[125]. The expression of key enzymes of COX-2 and AA metabolism increased in M1-type macrophages, while the expression level of COX-1 decreased. On the contrary, the expressions of COX-1 and AA-15 oxygenase increased in M2-type macrophages[126]. The mechanism diagram is shown in Fig. 5.

Table 3
Summary of metabolomics related to lipid metabolism in inflammatory cells.

Cell type	Model	Experiment	Methods	Amino acid species	References
RAW264.7	LPS	Vitamin D_3	Untargeted	Sphingolipid, amides, sphingosinols, sphingomyelin, palmitoyl	[58]
RAW264.7	LPS	Danhuanglian	Untargeted	Fatty acids	[64]
RAW264.7	LPS	3-Cinnamoyltribuloside	Untargeted	Choline, Ach	[67]
RAW264.7	LPS	Non-steroidal drugs	Untargeted	Eicosapentaenoic acid, DHA	[146]
RAW264.7	Knocking out the *STING* gene		Untargeted	Prostaglandin B1	[147]
RAW264.7	LPS	Puerarin	Untargeted	AA, 20-HETE, serotonin, Kyn, oxidized glutathione, γ-glutamylcysteine, cysteinylglycine	[148]
RAW264.7	Microplastics		Untargeted	Sphingolipid, sphingosine, 3-dehydrosphinganine	[149]
RAW264.7	LPS	Adropin	Untargeted	PPARγ	[150]
RAW264.7	LPS	Chuanwang Xiaoyan capsules	Untargeted	Phosphorylcholine	[62]
RAW264.7	Herpes simplex virus or vesicular stomatitis virus		Untargeted	11(12)-Epoxy-eicosatrienoic acids	[151]
RAW264.7	LPS		Untargeted	Phosphatidylserine (PS), phosphatidylethanolamine (PE), phosphatidic acid (PA), PC, PG, PI, ceramides	[152]
THP-1	Nicotine		Untargeted	Methylthioadenosine, cytosine, uric acid	[68]
THP-1	ox-LDL		Untargeted	Fatty acids	[76]
THP-1	LPS + IFN-γ	Quercetin	Untargeted	PC, PE, PI, PS, sphingomyelins	[113]
THP-1	ZnO, NPs		Untargeted	Choline, phosphocholine	[115]
THP-1	ox-LDL	NaPc	Untargeted	PGE2, glutathione	[153]
THP-1	Emamectin benzoate		Untargeted	Cantharidin, *D*-pyroglutamic acid, 3-succinoylpyridine, *N*-arachidonoyl dopamine, xanthosine and estriol 17-sulfate, purine	[154]
THP-1	LPS	Tetrahedral framework nucleic acid	Untargeted	Choline, phosphocholine, cytidine 5'-diphosphocholine	[155]

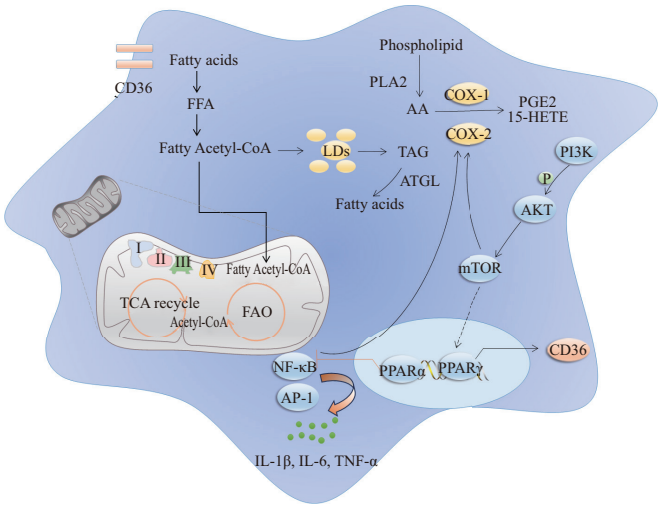

Fig. 5 Mechanism diagram of the process of fatty acid metabolism and associated inflammatory effects.

3.3.2 *Cholesterol metabolism*

Cholesterol metabolism is closely related to inflammation. Cholesterol synthesis is completed by a series of enzymatic reactions, with HMG-CoA reductase as the key enzyme. LPS can significantly increase intracellular cholesterol synthesis, whereas neither cholesterol levels nor cholesterol synthesis is increased in IL-4-induced M2-type macrophages[127]. In addition, LPS can reduce the expression of ATP-binding cassette transporter (ABCA1) and ABCG1 proteins in macrophages through the PPARγ/LXR pathway, reducing the efflux of cholesterol and resulting in cholesterol accumulation[128]. Cholesterol accumulation can activate the myeloid differentiation primary response 88 (MyD88)-dependent signaling pathway through TLR4, which in turn activates the NF-κB and p38 MAPK signaling pathways, leading to increased expression of pro-inflammatory cytokines[129-130].

Cholesterol metabolites are also involved in the inflammatory response. IL-4 and IL-13 induce the expression of cholesterol-25-hydroxylase (CH25H) through the transcription factor STAT6. Cholesterol is catalyzed by CH25H to produce 25-hydroxycholesterol (25-HC)[131]. The accumulated 25-HC in lysosomes competes with cholesterol for G protein-coupled receptor (GPR) 155 binding and inhibits the kinase mTORC1, leading to AMPKα activation and metabolic reprogramming[131]. 25-HC can also promote the activation of the TLR4, activate the NF-κB signaling pathway, and further aggravate the inflammatory response[132]. Bile acids, as a class of cholesterol derivatives, promote the serine phosphorylation of NLRP3 at position 291 through the TGR5-cAMP-PKA signaling axis in macrophages and promote the ubiquitination degradation of NLRP3, inhibiting the production of IL-1β[133]. PPARs are key nuclear factors that regulate proteins related to cholesterol metabolism and are involved in the regulation of lipid metabolism and the inflammatory response. PPARγ overexpression caused significant decreases in both extracellular and intracellular cholesterol[134]. PPARα is a nuclear transcription factor that regulates the expression of cytochrome P450 family 7 subfamily A member 1 (CYP7A1), and its activation enhances the transcription of *CYP7A1* gene, thereby promoting bile acid synthesis and maintaining cholesterol homeostasis *in vivo*[135]. The mechanism diagram is shown in Fig. 6.

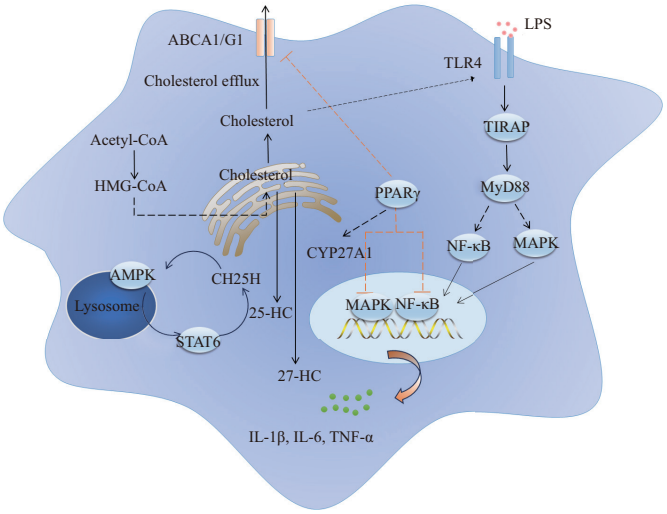

Fig. 6 Mechanism diagram of the process of cholesterol metabolism and associated inflammatory effects.

3.3.3 *Phospholipid and sphingolipid metabolism*

Phospholipids and sphingolipids are 2 important lipid components in biofilms that significantly affect cell function. Studies have shown that elevated levels of certain phospholipids, such as PC, are closely related to the phenotypic polarization of macrophages[136-137]. PC are important components of cell membranes and are involved in regulating cell signaling and inflammation. In an inflammatory environment, PC promotes the formation of M2-type macrophages, reducing inflammation[138]. PC can be broken down to release choline, which can be further used to synthesize acetylcholine (ACh). ACh binding with α7nAChR can significantly inhibit the release of intracellular calcium, down-regulate the activity of p38MAPK and NF-κB signaling pathway, and reduce the release of pro-inflammatory factors[139-140].

Sphingolipids are a class of lipids containing a sphingosine skeleton, which are widely present in cell membranes and participate in various biological processes. Sphingolipid metabolites such as sphingosine-1-phosphate (S1P) and ceramide-1-phosphate (C1P) play important roles in inflammation. Elevated levels of S1P at the site of inflammation can activate transcription factors STAT3 and NF-κB, regulate cytokine production, and promote inflammation[141]. S1P is involved in immune regulation by binding to S1P receptors, mediating the transport of immune cells and guiding lymphocytes from lymph nodes to circulation and target organs[142-143]. C1P can also stimulate macrophage migration through activation of MEK/ERK1-2, PI3K/Akt, and NF-κB signaling pathways, thereby regulating inflammatory cell function[144]. IL-10 signaling inhibits inflammation by regulating sphingolipid metabolism. In the absence of IL-10 signaling, macrophages exhibit increased metabolic flux through a novel sphingolipid biosynthesis pathway, leading to the accumulation of endogenous synthetic ceramides, which are critical for increased expression of inflammatory genes associated with IL-10 deficiency[145].

To summarize, lipid metabolism not only provides cells with essential substances and functions but is also closely linked to inflammatory processes. The activation of inflammatory signaling pathways disrupts lipid metabolism, thereby exacerbating the inflammatory response. These findings provide new perspectives and potential therapeutic targets for the treatment of inflammation-related diseases.

4. Conclusion and prospects

Metabolomics, as a powerful complement to other omics studies (genomics, proteomics), has established its important position in the entire field of life sciences and is widely applied in multiple areas. In current metabolomics research, serum, tissue, and fecal samples are widely analyzed for differential metabolites to uncover molecular mechanisms driving inflammatory processes[156-157]. With the rapid advancement of technology, the technical means of metabolomics research have been greatly enriched. Beyond traditional metabolomics techniques, emerging technologies such as spatial metabolomics, single-cell metabolomics (SCM), real-time *in vivo* metabolic monitoring, and high-throughput targeted metabolomic quantification are now extensively applied[158]. These techniques greatly improve the spatial resolution and sensitivity of the study, and overcome the limitations of traditional analysis of homogenate samples that lose key spatial information or mask cell heterogeneity.

The scope of metabolomics research has expanded from exploring disease biomarkers to understanding the mechanisms underlying phenotypes, and it has been integrated with different omics, such as genomics, transcriptomics, and proteomics, in an attempt to comprehensively investigate the roles and impacts of metabolites in biology. Therefore, to better meet current research needs, it is necessary to conduct statistical processing of multiple research samples and multivariate data, apply various detection technologies, and perform integrative analysis with multi-omics approaches. This approach not only facilitates the identification of inflammation-related metabolites and pathways within the body but also helps uncover the complex interplay between inflammation and other physiological processes.

In the treatment of inflammatory diseases, metabolic reprogramming has become a major focus in current life and basic medical research. Through integrative analysis with multi-omics, researchers can identify key factors affecting the metabolic reprogramming of macrophages and explore their specific mechanisms, providing potential new therapeutic targets and application values for anti-inflammatory therapies.

Declaration of competing interest

The authors report that there is no conflict of interest.

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