Regulation of fatty acid synthesis in immune cells

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Abstract
Metabolic reprogramming plays a critical role in the important cellular metabolic alterations that occur during the activation of immune cells to enable them to adapt to the extracellular environment. Here, we review recent studies on how substrate availability and metabolites mediate the signalling pathways that regulate fatty acid synthesis (FAS) in different immune cells and how FAS determines cellular fate and function. The major regulators sterol regulatory element-binding proteins and liver X receptors, the key enzyme ATP citrate lyase and the PI3K-Akt-mTOR signalling axis play important roles in de novo FAS during a variety of biological events, including cellular proliferation and differentiation and the development of organelles and intracellular membrane components in immune cells. In addition, the regulation of FAS substantially contributes to the inflammatory response of immune cells. Post-transcriptional modifications in FAS are also closely associated with the functional processes of immune cells. Understanding and investigating the intrinsic regulatory mechanism of FAS is of great significance for developing novel therapies for inflammation-induced diseases.

1 | INTRODUCTION

To protect the host from exogenous pathogens and foreign bodies, immune cells, including neutrophils, macrophages, and nature killer cells, form the first line of defence, called innate immunity. The innate immune system provides an immediate, generic response that activates adaptive immunity, the second line of defence, through antigen presentation. In contrast to other immune cells, antigen-presenting cells (APCs) such as dendritic cells (DCs), process the primary, digested antigens from neutrophils and macrophages and trigger the activation of T lymphocytes and B lymphocytes, two classes of specialized cells that belong to the adaptive immune response. Some of these adaptive immune cells differentiate into memory cells and regulatory cells, which regulate the initiation and development of the immune response and inflammation. One consequence of this immune response is the activation of immunometabolism in activated immune cells that were previously in a steady, quiescent state; most cell populations are relatively passive and quiescent.

Energy demand is essential for cellular function in both quiescent and activated cells. Oxidative phosphorylation and glycolysis are the two major pathways for energy production in cells. During their quiescent state, immune cells meet most of their energy demand via mitochondrial oxidative phosphorylation and catabolic metabolism, the same metabolic pathways used by normal cells. However, during the activation phase, anaerobic glycolysis is upregulated, even under conditions of sufficient oxygenation, to support an increase in fatty acid synthesis (FAS) and fatty acid oxidation (FAO). This upregulation in glycolysis has been defined as metabolic reprogramming. This phenomenon was first investigated by Otto Warburg and...
termed the Warburg effect. Cancer cells show increases in anaerobic glycolysis and the corresponding metabolites as well as in glucose uptake. Cancer cells rely heavily on this pathway to support cell viability and proliferation. In contrast to glycolysis upregulation due to disordered gene expression, metabolic reprogramming in activated immune cells, which are categorized as normal cells, resembles the Warburg effect. This metabolic reprogramming, which positions fatty acids as the major player in the metabolic adaption of the whole immunocyte, provides two insights: first, it depicts a relationship between immune cells and free fatty acid uptake as well as the crosstalk between immune cells and other cells, such as adipocytes, during fatty acid metabolic enrichment; second, it suggests that the intrinsic fatty acid metabolism within immune cells also regulates the immune response outcome.

In recent years, extensive studies have determined that the regulation of FAS is closely linked to the biological, physiological, and pathophysiological processes controlled by immune cells. The roles of complete metabolic alterations, including that of fatty acid metabolism, in T cells, DCs, and macrophages have been addressed in detail by several reviews. The role of fatty acid metabolism in T cells and Th17 cells has been extensively reviewed by Lochner and Wang. The subjects of the present review are the regulation of FAS by substrate availability or the metabolite-mediated signalling pathways of the above immune cells and how this determines cellular fate and function.

2 | FAS IN IMMUNE CELLS

Glycolysis and the citrate cycle are two integrated pathways that use glucose to satisfy the energy production needs of most cells, including immune cells. Glycolysis upregulation yields a large amount of pyruvic acid, most of which is converted into lactate and secreted into the extracellular space, but some pyruvate is decarboxylated by the enzyme pyruvate dehydrogenase (PDH) to generate acetyl-coenzyme A (acetyl-CoA) inside the mitochondria. Acetyl-CoA enters the citrate cycle to fuel the production of citrate, is consumed to produce the reduced form of nicotinamide adenine dinucleotide (NADH) and is then regenerated by a sequence of reactions that complete the cycle. NADH is fed into the oxidative phosphorylation pathway and respiratory chain to promote ATP synthesis. The citrate produced in this cycle is subsequently exported into the cytosol by mitochondrial citrate carriers encoded by solute carrier family 25 member 1 (SLC25A1) and is cleaved into oxaloacetic acid and acetyl-CoA by ATP citrate lyase. Oxaloacetic acid is further reduced to malate and replenishes the citrate cycle. Acetyl-CoA is used to promote FAS and for the construction of complex molecules such as cholesterol, phospholipids, and other active lipids. During FAS, two molecules of acetyl-CoA are converted into malonyl-CoA by acetyl-CoA carboxylase (ACC). Fatty acid synthase (FASN) then condenses acetyl-CoA and malonyl-CoA into palmitate or octadecanoic acid, and these de novo-synthesized lipids are used for the production of more complex lipid-containing substances.

In immune cells, fatty acids are used either as fuel for cellular metabolism through oxidation or as major components of membranes for cells or organelles such as the endoplasmic reticulum (ER) or Golgi body. Studies have also identified roles of fatty acids in the immune response and inflammation, that is saturated fatty acids promote inflammation, whereas polyunsaturated fatty acids exert anti-inflammatory effects. Fatty acid metabolism, including FAS in immune cells, is illustrated in Figure 1.

3 | FAS PATHWAY REGULATION IN IMMUNE CELLS

In immune cells, the major regulators of the FAS pathway are sterol regulatory element-binding proteins (SREBPs) and liver X receptors (LXRs). SREBPs are classified as nuclear transcription factors and are major regulators of key FAS enzymes in normal and tumour cells. In T cells, SREBPs also function as mediators in the feedback regulation of cholesterol synthesis and control lipid anabolism. In Homo sapiens, SREBPs are encoded by two genes, srebf1 and srebf2, with three isoforms, SREBP-1a, SREBP-1c, and SREBP-2. All three SREBPs potentially affect lipid biosynthesis by regulating FAS gene expression, controlling lipid movement or targeting both of these processes. Their activities are tightly associated with SREBP cleavage-activating protein (SCAP), which mediates SREBP transport and proteolytic cleavage through binding. The depletion of SCAP inhibits SREBP activities in T cells. LXRs are nuclear receptors that control cholesterol synthesis and FAS. LXRs regulate genes involved in the processes of lipid exocytosis, cholesterol trafficking and fatty acid structural modifications; for example, the genes abca1, abcg1, and apoe encode lipid transport proteins, and elovl5, fads2, scd1, and scd2 encode enzymes involved in fatty acid remodelling. LXRs can also inhibit other signal-dependent transcription factors, such as AP-1 and NF-κB, and can activate genes encoding anti-inflammatory proteins, such as the receptor tyrosine kinases TYRO-3, AXL, and MER (TAM), and molecules that promote the synthesis of anti-inflammatory polyunsaturated fatty acids. The knockout of LXRs leads to the rapid accumulation of macrophages and increases atherosclerosis, whereas LXR overexpression or synthesized LXR activators ameliorate lipopolysaccharide...
**FIGURE 1** Fatty acid metabolism in immune cells. Immune cells uptake glucose and upregulate the glycolysis. Most glucose-derived pyruvate are converted into lactate and secreted into extracellular surroundings, while some enter the mitochondria where it is first converted to acetyl-CoA and then to citrate through the citrate cycle. After it is transported into the cytosol, the cytosolic citrate can be cleaved into oxaloacetic acid and then further reduced to malate for replenishing the citrate cycle. It can also be reconverted to acetyl-CoA that is used to drive the fatty acid synthesis, and further constructs complicated physiological substances such as cholesterol, phospholipids and other active lipids, which either are fueled for cellular metabolism through fatty acid oxidation or used as the major components of cytomembrane or organelle membrane such as endoplasmic reticulum or Golgi body. Meanwhile, they demonstrate important roles in immune response and inflammation (LPS)-induced inflammation. The immunobiological function of LXRs in immunocytes has been extensively discussed by Spann et al.

The impact of the PI3K (phosphoinositide 3-kinase)-Akt (serine/threonine kinase, also known as protein kinase B)-mTOR (mammalian target of rapamycin) signalling axis on the activation and key enzymes of FAS has been illustrated in liver cells and adipocytes. The expression of this pathway’s regulators enhances the expression of SREBPs, leading to the enrichment of SREBPs on the promoter loci of *acaca* (encoding ACC), *acly* (encoding ATP citrate lyase, ACLY), and *Fasn* (encoding FASN) and ultimately inducing upregulation of the entire FAS pathway. Akt can also directly phosphorylate ACLY and ACC as another regulatory mechanism of FAS. However, the role of the PI3K-Akt-mTOR pathway has not been fully validated in immunocytes.

Toll-like receptors (TLRs) increase glycolysis via signalling by the TANK-binding protein (TBK1) and IkappaB kinase epsilon (IKKe). DC activation is dependent on the glycolysis-induced promotion of the FAS pathway to support the expansion of its cytomembrane. This upregulation of FAS is not related to peroxisome proliferator-activated receptor (PPAR) because roglitazone, a PPARγ sensitizer, cannot compensate for LPS-induced deficient DC activation when FAS is inhibited. Figure 2 demonstrates the regulatory pathway of FAS in immune cells.

Effector molecules such as interferons (IFNs) and interleukins (ILs) also participate in metabolic reprogramming and FAS. In plasmacytoid DCs, the autocrine agent IFN-α is upregulated by TLR-9 activation, resulting in enhancement of oxidative phosphorylation and FAO. Within cells, FAO is highly dependent on fatty acids obtained from de novo FAS, as evidenced by the finding that the administration of 5-tetradecyloxy-2-furoic acid (TOFA, an inhibitor of ACC) or C75 (an inhibitor of FASN) represses the activity of oxidative phosphorylation and FAO and further influences the activation of these cells. These observations also support the theory that intrinsically synthesized fatty acids constitute the main supply source for FAO. A study in macrophages illustrated that IFN-β can suppress both FAS and cholesterol biosynthesis via repression of SREBPs. In a murine model of alcoholic fatty hepatitis, an antibody against IL-17, a specific marker of Th17 cells,
significantly inhibited FAS in the liver by suppressing SREBP and carbohydrate response element-binding protein (CHREBP), which is also a direct regulator of FAS. However, this study did not validate the location of the above-mentioned regulators in hepatic tissue. In an in vivo investigation of haemorrhagic shock, C75, a validated inhibitor of FASN, suppressed the expression of IL-6 and ameliorated organ injury. CD137 (TNF receptor super family member 9 or 4-1BB) signalling activated FAS via the LKB1 kinase-AMP-activated protein kinase (AMPK)-ACC pathway and enhanced the proliferation of CD8+ T cells. All these studies support an important association between the FAS pathway and immune-related molecules, such as IFNs and ILs. Further studies in this field might unveil a complex network of immuno-metabolism and immune responses.

In addition to glycolysis, other metabolic pathways can regulate FAS activity in immune cells. A recent study defined a role of indoleamine 2,3-dioxygenase (IDO) in the kynurenine pathway of CD4+ cells. IDO activates general control nonderepressible 2 kinase and further reduces the expression of FAS enzymes, thus impairing the proliferation and differentiation of CD4+ effector cells. Isocitrate dehydrogenase (IDH), which participates in glutamine catalysis, is driven by the capicua transcriptional repressor (CIC) and the sustained production of reduced nicotinamide adenine dinucleotide phosphate (NADPH), and a biological relationship has been identified between IDH and FAS. These results provide further insights on the crosstalk between glutamine metabolism and FAS in macrophages and T lymphocytes.
4 | REGULATION OF FAS IN DIFFERENT IMMUNE CELL SUBSETS

4.1 | FAS regulation in T cells

T cells in quiescence mainly rely on oxidative phosphorylation and FAO to satisfy their energy demands. However, the intrinsic glycolysis and FAS pathways are enhanced after T cell activation.

The mTOR-SREBP pathway plays a vital role in the regulation of FAS and is the link between T cell activation and FAS. In CD8+ T cells, the mTOR-SREBP pathway regulates FAS, as evidenced by the ability of rapamycin, a known inhibitor of mTOR, to significantly suppress the de novo lipogenic pathway. mTOR is a serine/threonine kinase that regulates cellular metabolism by mediating multiple exogenous and endogenous signals. Consistent with the ability of mTOR to regulate the FAS pathway in other cell types, recent studies have validated the regulatory function of mTOR in FAS in T cells. FAS activity can be completely inhibited by knocking out regulatory-associated protein of mTOR complex 1 (Raptor), an important subunit responsible for the assembly and localization of the mTOR complex. This mTOR-mediated regulation of FAS has also been found to be associated with SREBP localization and enrichment on the gene promoter loci of lipogenic enzymes, such as acaca and fasn, after the activation of murine CD8+ T lymphocytes. The enrichment of SREBPs and the associated downstream upregulation of FAS were both sensitive to inhibitors of PI3K and mTOR, and the knockout of Raptor severely downregulated the expression of SREBP-1 and SREBP-2. SCAP knock-in inactivated SREBP signalling and further influenced the proliferation, development, and differentiation of CD8+ T cells. In contrast to its important regulatory role in cancer cell proliferation and survival, SREBP activity did not appear to affect the proliferation and homeostatic maintenance of CD8+ T cells. Recent experiments have illustrated that the inhibition of lipogenic enzymes either by specific enzyme inhibitors or by knockout of encoding genes blocks the differentiation and development of T cells. Therefore, it is speculated that FAS may serve as a metabolic assessor in T cell development and differentiation rather than functioning as a metabolic determinant.

Memory CD8+ T cells are dependent on de novo FAS rather than the exogenous uptake of lipids. AMPK-regulated CD8+ T cell memory formation relies on FAO using distinct sources of lipids in different cell subsets. In the effector clusters of CD8+ T cells, sufficient fatty acid uptake facilitates oxidation reactions. In contrast, Sullivan et al declared that memory CD8+ T cells utilize only intrinsic fatty acids. In their study, glycolysis increased FAO and oxidative phosphorylation reactions, and the intrinsic fatty acids used for oxidation were mainly located in the lysosome, although the source of the fatty acids inside the lysosome was unclear. Two hypotheses have been proposed to explain this situation. The first is that because glycolysis upregulates FAO and oxidative phosphorylation, extensive FAS activity has already been conducted in the preliminary stages of CD8+ memory cell development, and the synthesized fatty acids are stored in the lysosome for oxidation at later time points. Another hypothesis is the following: because free fatty acids are toxic to cells, CD8+ T cells, following the extensive uptake of exogenous fatty acids, may use lysosomes as an intrinsic reservoir and then oxidize the stored fatty acids after cell memory formation. This issue requires further clarification.

In CD4+ T cells, FAS is not only linked to cell development but has also been shown to affect the immune response. The processes of FAS and FAO collaborate to determine cell fate or facilitate the development of cells into either regulators or effectors. CD4+ T cells are classically categorized as Th1, Th2, Th17, or CD4+Foxp+ T cells according to their surface markers or are classified as regulatory T cells (Tregs), helper T cells, memory T cells or effector T cells according to their immunobiological function. The activation of mTOR is an important event for CD4+ T cells. Several studies have illustrated that the knockout of different components of the mTORC complex has distinct impacts on different subsets of CD4+ T cells. In detail, Ras homologue enriched in brain (Rheb), the catalytic subunit of mTORC, is essential for cell differentiation towards Th1 or Th17 rather than Th2, whereas RPTOR independent companion of mTOR complex 2 (Rictor), promotes differentiation toward Th2 rather than Th1 and Th17. However, the underlying mechanism remains poorly understood. In Th1, Th2, and Th17 cells, mTOR is also a major sensor and regulator of cellular metabolism signalling because it induces enhanced expression of glucose transporter 1 (GLUT1) in the glycolytic pathway. In Th17 cells, the inhibition of ACC1, which produces malonyl-CoA as a building block for new fatty acids, is a severe obstacle for cell development. Although metabolic reprogramming has been observed in all three T cell subsets, the role of FAS has been substantially investigated only in Th17 cells. After Th17 cell activation, upregulation of the glycolysis-citrate cycle-FAS axis promotes stringent de novo FAS to satisfy the massive energy demand mainly via the glycolysis-driven FAS pathway rather than the uptake of exogenous lipids. FAS also plays an extended role in affecting the immune response of Th17 cells, which commonly play dual roles in the physiological immune response and autoimmunity. Subsequent studies have demonstrated that both ACC1 and FASN participate in the regulation of pathogenicity in Th17 cells.
Recently, Wang et al proposed an FAS-related mechanism for regulating this balance. These researchers discovered that CD5 molecule like/Apoptosis inhibitor of macrophage (CD5L/AIM) signalling not only regulates both the ratio of polyunsaturated fatty acids (PUFAs) to saturated fatty acids (SFAs) and FAS-based cholesterol synthesis but also affects retinoid-related orphan nuclear receptor γt (RORγt), a member of the nuclear receptor family of transcription factors, in a ligand-dependent manner. Taken together, these findings suggest important biological roles for FAS in CD4+ T cell regulation.

The above studies were performed in vitro, and in vivo, a more sophisticated metabolic regulatory pathway has been suggested for T cell activation. Glick et al proposed an in vivo model that provided insights on the complicated interactions among the metabolic pathways in activated T cells. These researchers observed that FAO inhibited glycolysis in vivo, and high FAO activity increased the NADH/NAD1 and ATP/AMP ratios in the cytosol and mitochondria. The mitochondrial concentrations of acetyl-CoA and citrate were also increased. IDH was inhibited by NADH and ATP, resulting in suppression of the citrate cycle and an increase in the export of citrate into cytosol. Enhanced anaplerosis by citrate lyase produced oxaloacetate to resupply the citrate cycle and acetyl-CoA (another by-product of this reaction) to fuel FAS. However, additional investigations beyond this unique preliminary study distinguishing between the metabolism of activated T cells in vitro and in vivo are essential for further interpretation in this field.

4.2 | FAS regulation in macrophages

Activated macrophages are routinely classified as either M1 or M2 according to their immunobiological function. Studies of the metabolic pattern of each type have demonstrated that the M1 phenotype primarily relies on glycolysis (CD5L/AIM) signalling not only regulates both the ratio of polyunsaturated fatty acids (PUFAs) to saturated fatty acids (SFAs) and FAS-based cholesterol synthesis but also affects retinoid-related orphan nuclear receptor γt (RORγt), a member of the nuclear receptor family of transcription factors, in a ligand-dependent manner.64 Taken together, these findings suggest important biological roles for FAS in CD4+ T cell regulation.

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The key enzymes of FAS not only produce sufficient fatty acids for the development and differentiation of macrophages but also participate in macrophage-mediated inflammation. ACly, the primary enzyme responsible for the synthesis of cytosolic acetyl-CoA, is a substantial prerequisite for macrophage-mediated inflammation. In activated macrophages, mRNA and protein expression are enhanced, and ACly inhibitors decrease important inflammatory modulators such as nitrogen oxide, reactive oxygen species, and prostaglandin E2. Kim et al found that curcumin activates AMPK and promotes the phosphorylation of downstream ACC in macrophages, thereby relieving lung injury. FASN has also been suggested to participate in the composition of the cellular membrane via the synthesis of fatty acids by the enzyme itself. FASN deficiency could lead to impairment of membrane order and inflammatory signalling. However, the impaired membrane but not inflammatory signalling could be partly rescued by providing exogenous fatty acids under the condition of inhibited FASN. The above results indicate that FASN is mitochondrial. Uncoupling protein 2 is upregulated in both patients and murine models of sepsis and mediates the expression of NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasomes via modulation of FASN, whose regulatory function is highly dependent on the Akt and p38 MAPK signalling pathways. Recent studies have suggested a role for NLRP3 inflammasomes and their key component, gasdermin D, in pyroptosis, a novel form of programmed cell death. A study in renal tissue found that the NLRP3 inflammasome is inhibited by resveratrol, a strong FASN inhibitor. Thus, the role of FASN or FAS in the pyroptosis pathway requires further investigation. Interestingly, activation of the the NLRP3 inflammasome promotes secretion of IL-1β and IL-18 and the maturation of these cytokines is linked to SREBPs. Validating the relationship between SREBPs and NLRP3 inflammasome is a worthwhile future research direction.

4.3 | FAS regulation in DCs and B cells

DCs are capable of recognizing micro-organisms and are the most important APCs because they mediate immune responses and induce immune tolerance. DCs can be categorized into distinct subsets based on their phenotype, microenvironmental localization, or function (eg
conventional DCs vs plasmacytoid DCs or tolerogenic DCs vs immunogenic DCs.)

Early studies in tumour-derived DCs indicated that lipid accumulation leads to cell differentiation towards immunologic tolerance and that ACC inhibitors can partially restore the function of DCs.29 Rehman et al demonstrated that FAS participates in the differentiation and development of DCs and is closely associated with DC immune phenotype and morphology. Inhibiting the FAS pathway has different effects on the expression of TLRs that recognize specific patterns on micro-organisms, such as suppressing TLR2 and TLR4 or enhancing TLR7 and TLR9. FAS eliminates ER stress by upregulating PPARγ, further expanding the antigen-capture potency of the cell. Inhibiting FAS also increases the activating capacity of DCs toward other immune cells, such as T cells and natural killer cells (NK cells).80 However, in another study, upregulating FAS only facilitated expansion of the cell and Golgi membranes of plasmacytoid DCs rather than affecting cytokine secretion or the immune phenotype.8 In tumour-derived DCs, oxidized lipids accumulated, and the ER stress level was increased via inositol-requiring enzyme-1α (IRE1α), resulting in consistent activation of X-box-binding protein 1 (XBP1) and further blunting the function of DCs by promoting FAS and lipid storage in DCs.81,82 The knockdown of XBP1 resulted in enhanced immunogenicity and further activation of protective immune reactions in tumours. These results appear contradictory to the physiological function of XBP1 in DCs. Further studies focusing on XBP1 mutations and alterations in its epigenetic control or regulatory factors are needed to address this discrepancy. These conflicting studies imply that the intrinsic mechanism through which FAS participates in cell development and governs immunity, although poorly understood, might be quite sophisticated. It can at least be proposed that the functions of FAS vary among different subsets of DCs and might mediate the communication between DCs and other immune cells.

B cells can also present antigens and are regarded as APCs, although their primary role is in humoral immunity through the secretion of antibodies. Rocketts found that n-3 PUFAs altered the composition of the B cell cytomembrane surface lipidome.83 Brewer et al84 have discussed in detail the relationship between XBP1 and lipogenesis, including the mechanism through which XBP1 initiates a cascade of biochemical events, including FAS stimulation, in response to the demand for membrane protein and lipid components in activated B cells. In B cells, the roles of key enzymes in the FAS pathway were revealed by Dufort et al, who indicated that ACLY plays a critical role in de novo lipogenesis in LPS-induced B cell differentiation. The inhibition of ACLY activity impairs FAS, including the synthesis of cholesterol, free fatty acids, neutral and acidic phospholipids, and suppresses cell proliferation and the phenotypic differentiation of plasma-like B cells.85

5 | POST-TRANSCRIPTONAL MODIFICATIONS IN FAS

One relevant question prompted by the above discussion is whether the substrates and intermediates of FAS directly impact the development and differentiation of immune cells. Acetyl-CoA is the substrate of acetylation, one of the most studied modifications in immune cells, and is also utilized as the initial substrate of the FAS pathway. Because ACLY is an important enzyme in FAS, its post-transcriptional modifications have been studied in depth, and these studies have revealed that its regulation is closely associated with histone acetylation in immune cells. Below, we briefly summarize discussions of acetylation and its immunobiological role in immune cells.

ACYL is the major enzyme responsible for acetyl-CoA production and is located in both the cytosol and nucleus.86 ACLY degrades citrate and produces acetyl-CoA in the nucleus, which serves as the substrate for histone acetyltransferases (HATs). HATs acetylate histones to facilitate the binding of RNA polymerase and the transcription of relevant genes by loosening the tightly coiled structure of chromatin and histones.86 Tip60 and p300 are representative HATs in immunocytes.87,88 Histone deacetylases (HDACs) are a class of enzymes that perform histone deacetylation. HDACs such as HDAC1-HDAC11 and Sirt1-Sirt7 have the opposite action of HATs and repress gene transcription. Acetylation also stabilizes the ACLY enzyme and protects it against ubiquitination. HATs (p300) and HDACs (Sirt2) participate in the acetylation and deacetylation of this enzyme in tumour cells.89 However, whether this regulatory mechanism is also present in immune cells remains unknown.

Interestingly, ACLY is upregulated during the FAS-facilitated differentiation of Th17 cells but not Tregs, indicating a distinctive effect of histone acetylation in these cell types.5 Moreover, the specific loci of chromatin containing the signature Th17 genes have been described as hyperacetylated, and cytokines can regulate downstream effectors in a similar manner. For example IL-12 induces chromatin reconstruction at the locus where the *IFNG* gene is found, whereas IL-4 increases histone acetylation at the promoter regions of *IL13, IL15*, and *IL4*90; both cytokines upregulate gene transcription.

Proteins involved in immune response modulation are also targets of acetylation. Foxp3 can be acetylated at distinct lysine residues by Tip60 and p300, whereas the HDAC members HDAC6, HDAC9, and Sirt1 catalyse deacetylation.91 Acetylation of Foxp3 modifies its capacity...
to bind specific DNA regions, such as the promoter region of IL2. Foxp3 acetylation stabilizes this protein by protecting it from ubiquitination and subsequent proteasomal degradation.\(^92\) The importance of Foxp3 acetylation in the murine model was validated with a specific knockout of the HAT.\(^93\)

In macrophages in general and M2 macrophages in particular, IL-4 mediates ACLY phosphorylation through Akt-mTOR signalling by altering the expression of genes responsible for cell development, checkpoint, and polarization via histone acetylation.\(^40\) The relationship between HATs and HDACs in the macrophage immune response has been reviewed in detail by Baardman et al.\(^94\), who clearly showed links for epigenetic function with altered macrophage metabolism, macrophage activation, and disease.

### 6 CONCLUSION AND REMARKS

FAS is an integral component of the dynamic metabolism of immune cells and can be influenced by the global metabolic state and by exogenous signals. Recent studies of immunocytes have revealed that a series of biological events, including cell development and differentiation and the immune response, are either directly or indirectly under the influence of FAS and its enzymes. Understanding the role of FAS participation in the immune response, which is governed by distinct types of immune cells, is a challenging task. Numerous studies have investigated the interaction between and the detailed mechanism of the effector molecules and FAS in immunocytes. Another critical issue is the biological influence of FAS on post-translational modifications, which might contribute to the signalling responsible for modulating FAS and its key enzymes. Because the role of metabolic reprogramming has been validated in critically ill patients and the metabolomic signatures of these patients are consistent with findings in cell and animal models, similar manipulation strategies might improve patient outcomes.\(^95\) In summary, a better understanding of the immunobiological roles of key FAS enzymes and their regulators could pave the way for developing novel strategies for targeting immune-relevant diseases such as sepsis and atherosclerosis.

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### CONFLICT OF INTEREST

All authors declare that they have no relevant conflicts of interest in this study.

### AUTHOR CONTRIBUTION

Xuchen Qian performed the literature review, thoroughly read the referenced literature and wrote the manuscript. Zhi-tao Yang and Enqiang Mao revised the manuscript for content and language. Erzhen Chen devised the study proposal, revised the manuscript, and supervised the entire study.

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