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Review

Immunomodulatory properties of mesenchymal stromal/stem cells: The link with metabolism

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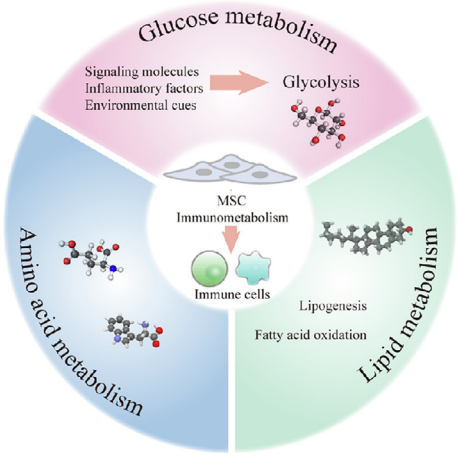
HIGHLIGHTS

- Metabolism plays critical roles in the MSCs immunomodulatory properties.
- Manipulation the metabolism in MSCs can enhance their therapeutic effects.
- MSCs can affect the immune cells metabolism and determine their behaviors.
- The more direct evidence of MSCs immunometabolism is needed to be uncovered.
- The mechanism of metabolism influencing immunomodulatory properties in MSCs is unclear.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Mesenchymal stromal/stem cells (MSCs) are the most promising stem cells for the treatment of multiple inflammatory and immune diseases due to their easy acquisition and potent immuno-regulatory capacities. These immune functions mainly depend on the MSC secretion of soluble factors. Recent studies have shown that the metabolism of MSCs plays critical roles in immunomodulation, which not only provides energy and building blocks for macromolecule synthesis but is also involved in the signaling pathway regulation.

Aim of Review: A thorough understanding of metabolic regulation in MSC immunomodulatory properties can provide new sights to the enhancement of MSC-based therapy.

Key scientific Concepts of Review: MSC immune regulation can be affected by cellular metabolism (glucose, adenosine triphosphate, lipid and amino acid metabolism), which further mediates MSC therapy efficiency in inflammatory and immune diseases. The enhancement of glycolysis of MSCs, such as signaling molecule activation, inflammatory cytokines priming, or environmental control can promote MSC immune functions and therapeutic potential. Besides glucose metabolism, inflammatory stimuli also alter the lipid molecular profile of MSCs, but the direct link with immunomodulatory properties remains to be further explored. Arginine metabolism, glutamine-glutamate metabolism and tryptophan-kynurenine via

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indoleamine 2,3-dioxygenase (IDO) metabolism all contribute to the immune regulation of MSCs. In addition to the metabolism dictating the MSC immune functions, MSCs also influence the metabolism of immune cells and thus determine their behaviors. However, more direct evidence of the metabolism in MSC immune abilities as well as the underlying mechanism requires to be uncovered.

Introduction

Stem cells including pluripotent embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and tissue-resident adult stem cells (ASCs), are characterized by the capacities of self-renewal and multipotent differentiation. The application of ESCs and iPSCs is greatly restricted due to the ethical issues and the risk of tumor formation. In this context, ASCs are widely used in stem cell-based therapy for tissue regeneration and repair in the clinic. Mesenchymal stromal/stem cells (MSCs) including the bone marrow, adipose tissue and umbilical cord-derived MSCs are most commonly used in stem cell-based therapy. In addition to differentiating into resident cells to replace the injured tissues, MSCs possess potent immunomodulatory properties to regulate the adjacent cells and empower the tissue repair, which have been well demonstrated in various disease treatments, such as lung injury, arthritis, colitis, acute graft versus host disease (GVHD) et al [1–3]. In fact, the immunomodulation of MSCs is mainly achieved by autocrine and paracrine secretion including releasing variant immunoregulating cytokines or extracellular vesicles, which has been reviewed elsewhere [1,4].

Recent evidence has proven that the immune regulation of MSCs could also be affected by metabolism, which not only provides energy and building blocks for macromolecule synthesis but is also involved in the signaling pathway regulation. Environmental stimuli induce metabolic alteration and subsequently influence the MSC immune capacities and repair abilities in inflammatory and immune diseases. Manipulations of the MSC metabolism, such as gene or enzyme regulation, cytokines priming, or environmental control, serve as promising and feasible targets to enhance MSC immunomodulation and therapeutic effects. Therefore, a thorough understanding of MSC immunometabolism and subsequent explorations of the possible mechanism are prerequisites.

In this review, we comprehensively focus on the glucose, adenosine triphosphate (ATP), lipid and amino acid metabolism in MSC immunomodulatory functions. At the same time, we exhibit how the mentioned metabolisms mediate the MSC therapy efficiency in various inflammatory and immune diseases. Then, we also describe how MSCs regulate the metabolism of the immune cells to dictate their functions in disease therapy. Finally, we discuss the clinical application of MSCs in the regenerative field.

Glucose metabolism

The main energy metabolism is glucose catabolism, of which glycolysis is the extraordinarily critical part, occurring in the cytosol. Following a series of redox reactions, the main terminal products of glycolysis are pyruvate and ATP molecules. In most cell types, the pyruvate can be further broken down into lactate via lactate dehydrogenase (LDH) or into acetyl-CoA via pyruvate dehydrogenase (PDH). The manipulation of these two dehydrogenases to shunt pyruvate into distinct flux determines the stem cell fate [5]. Furthermore, the intermediates in glycolysis can also be shunted into amino acid, lipid and nucleotide synthesis to link the energy metabolism. Recent studies have demonstrated that the enhancement of glycolysis of MSCs elevated their therapeutic effects in diseases including cardiovascular diseases, bone defect disease and ischemic disease by promoting survival after transplantation [6,7], upregulating the proliferation and differentiation capacities [8] or increasing the secretion of pro-growth factors [9] for tissue regeneration.

Beyond regulating MSC proliferation and differentiation, glycolysis is reported to improve and maintain MSC immune function. The immunomodulatory activation of MSCs is not constitutive but licensed by exogenous stimulation, such as pro-inflammatory cytokines (IFN-γ, TNF-α, LPS) and hypoxia. This enhanced immunomodulatory capacity of MSCs requires a metabolic switch towards glycolysis (reducing the TCA cycle). As demonstrated by R. Contreras-Lopez, MSCs pretreated with oligomycin (a known inhibitor of ATPase and oxidative phosphorylation (OXPHOS) metabolism) exhibited an increment of extracellular acidification rate (ECAR) (an indicator of aerobic glycolysis) and a down-regulated oxygen consumption rate (OCR), which was associated with HIF-1α expression, consequently resulting in inhibition of pro-inflammatory Th1 and Th17 proliferation and increase of the Treg cell population, explaining the therapeutic potentials of MSCs in the Delayed-Type Hypersensitivity (DTH) murine model [10]. Likely, co-culture with peripheral blood mononuclear cells (PBMCs) promoted the glycolytic activity of MSCs, which was accompanied by enhanced suppression of T cell proliferation [11]. Glycolysis augmentation provides an emerging avenue to improve the immunomodulatory properties of MSCs. Strategies that can promote glycolytic metabolism such as signaling molecular regulation, inflammatory factors stimulation and external environmental manipulation facilitate MSC immune properties and thus enhance therapeutic efficiency (Fig. 1).

Signaling molecules regulate glycolysis-associated immunomodulation

Mammalian target of rapamycin (mTOR)

mTOR, an evolutionary conserved serine-threonine kinase serves as a sensor of numerous stimulations such as O_2, nutrients, and growth factors. Recently, its role in regulating metabolism to promote MSC immune functions has provoked great interest. Accumulating evidence has revealed that activation of the mTOR signaling pathway facilitates a switch in glucose metabolism from OXPHOS to glycolysis, which enhances MSC immunosuppressive capacities. As clarified by Y. Liu et al, the PI3-kinase/AKT signaling cascade and its downstream effector mTORC1 mediated the metabolic shift to glycolysis in IFN-γ treated MSCs, increasing the production of immune-regulatory factors (indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2 (PGE2)). However, the mTOR inhibitor, rapamycin, which was an immune-suppressive drug applied in the clinic reversed this effect [11]. Additionally, the AMP-activated protein kinase (AMPK), a cellular energy sensor, which supported the ATP supply, served as the upstream of mTOR and was also involved in the immunometabolism regulation of MSCs. Recent research conducted by R. Contreras-Lopez et al demonstrated that AMPK signaling pathway mediating glycolytic reprogramming of MSCs, enhanced the immunosuppressive functions and increased therapeutic benefits in the DTH and the GVHD murine models [12]. Mechanically, mTOR induced glycolysis flux by targeting two critical transcription factors: HIF-1α and myelo-

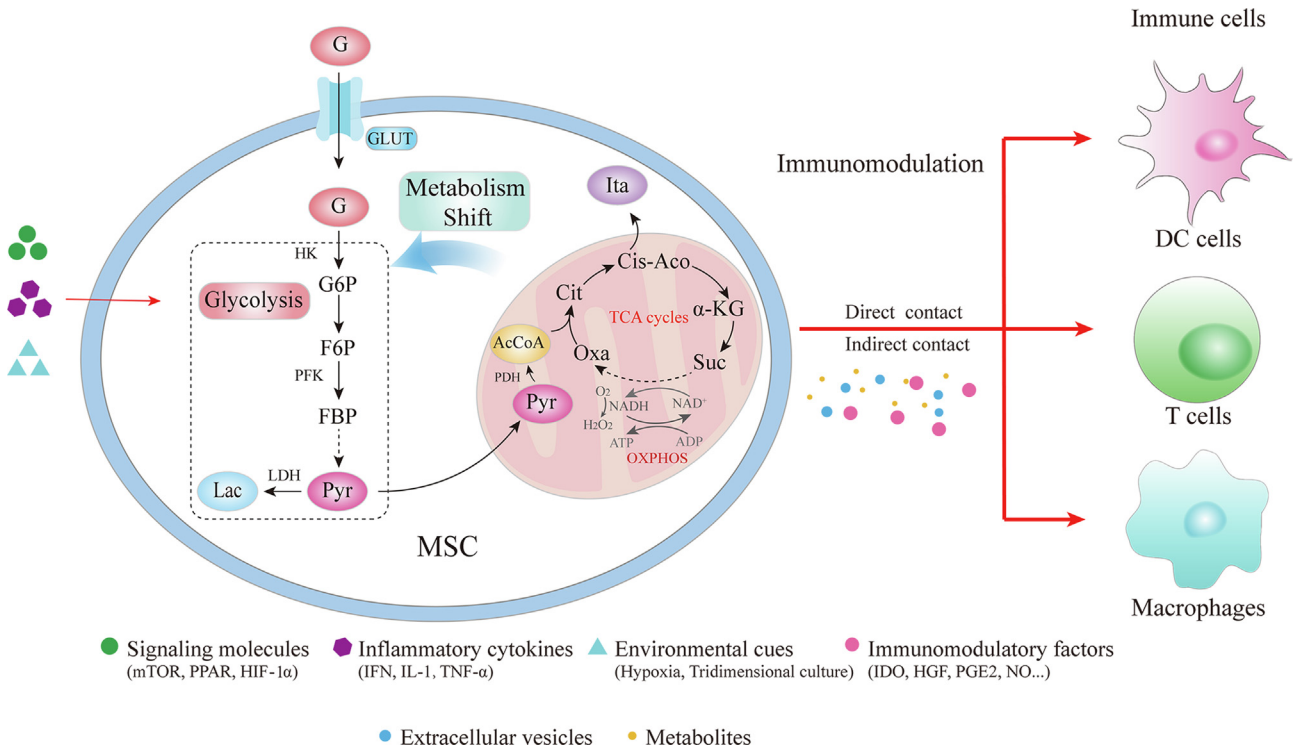

Fig. 1. Glucose metabolism in MSC regulating immunomodulation. Signaling molecules, inflammatory cytokines and environmental cues can enhance the metabolic shift from OXPHOS to glycolysis in MSCs and thus promote the immunoregulatory capacities. The effect of MSCs on immune cells can be achieved by direct cell–cell contact or releasing metabolites and secretomes including immunomodulatory factors, extracellular vesicles. G, glucose; GLUT, glucose transporters; HK, hexokinase; G6P, glucose-6-phosphate; F6P, fructose-6-phosphate; PFK, phosphofructokinase; FBP, fructose bisphosphate; Pyr, pyruvate; Lac, lactate; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; AcCo, acetyl-CoA; Cit, citrate; Cis-Aco, *cis*-Aconitate; Suc, succinate; Oxa, oxaloacetate; Ita, Itaconate; TCA, tricarboxylic acid.

cytomatosis oncogene (c-Myc). mTORC1 enhanced the abundance of HIF-1α protein under hypoxia and increased the transcriptional activity of HIF-1α by S6K1/S6 and eukaryotic initiation factor 4E (eIF4E) binding protein 1 (4EBP1)/eIF4E pathways or by promoting the interaction of HIF-1α with the transcriptional co-activator p300 [13–15]. HIF-1α promoted glycolysis through activation of glycolytic enzymes (such as glucose transporters (GLUT1) and glucose-6-phosphate transporter (G6PT)) [16] and through inhibition of mitochondrial respiration by targeting pyruvate dehydrogenase kinase 2 (PDK2) and PDK4 to suppress PDH and shunt pyruvate flux to lactate [17]. Using a novel chemically synthesized sphingosine metabolite, o-cyclic phytosphingosine-1-phosphate (cP1P), activated mTOR-HIF-1α signaling pathway, contributing to glycolysis enhancement and therapeutic improvement of MSCs [15]. On the other hand, c-Myc, a potent oncogene, well-known for its ability to boost glycolytic metabolism and glutaminolysis [18], regulated the critical glycolytic genes (GLUT1, LDH, pyruvate kinase type M (PKM) and hexokinase (HK)2) and glutamine transporters proteins, which were required for T cell proliferation and activation. Deletion of Myc inhibited the glycolysis and thus suppressed T cell proliferation [19]. mTOR-Myc axis played critical roles in metabolic associated immunomodulation [20] in immune cells, however, little was known regarding its roles in MSC metabolism regulation and immunomodulation.

Peroxisome proliferator-activated receptor (PPAR)

PPAR family members are nuclear-receptors consisting of PPARα, PPARβ/δ and PPARγ, ubiquitously expressed in MSCs, serving as transcription factors upon ligand activation and initiating cell transcriptional programming. PPAR plays important roles in lipid metabolism. In general, PPARα and PPARβ/δ are responsible for fatty acid oxidation (FAO) through participating in substrate delivery and OXPHOS while PPARγ focuses on lipogenesis [21]. Evidence indicated that PPARγ was identified to block the osteogenic differentiation and promote the adipogenic differentiation of MSCs while PPARβ/δ was found to induce osteoblast differentiation by the Wnt signaling pathway [22]. Not surprisingly, inhibiting the PPARγ pathway in periodontal ligament stem cells (PDLSCs) using the cannabinoid receptor I (CB1) promoted MSC osteogenesis and enhanced their regeneration in periodontitis [23]. Interestingly, B.E. Heck et al exhibited that PPARδ agonist alleviated the osteoarthritis (OA) by enhancing the MSC chondrogenesis and blunting the inflammation. The mix of PPARδ agonist, hyaluronic acid (HA) gel and bone marrow mesenchymal stromal/stem cells (BMSCs) significantly rescued the formation of type II collagen cartilage in the human OA synovial fluid [24].

Additionally, PPAR also regulated glucose metabolism. The emerging research has found that the PPAR affected the glycolysis in MSCs and thus regulated their immunosuppressive properties and therapeutic efficiency [25]. For example, Contreras Lopez et al unveiled that PPARβ/δ invalidation switched MSC metabolic state towards glycolysis, which promoted the inhibition of Th1 and Th17 proliferation [26]. Compared with PPARβ/$\delta^{+/+}$ MSCs, the glycolytic-associated factors including the ratio of ECAR to OCR, the glucose consumption, lactate production as well as the GLUT1 expression level significantly elevated in PPARβ/$\delta^{-/-}$ MSCs, contributing to immune function enhancement. In line with this, Luz-Crawford et al reported that PPARβ/δ deficiency dictated immunosuppressive and therapeutic properties of MSCs in arthritis through increasing vascular cell adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1 and nitric oxide (NO) production [3].

Although the critical roles of PPAR in the immune system have been well-reviewed elsewhere [21], the direct evidence of

PPAR-mediated MSC immunometabolism (either glucose or lipid metabolism or both) is deficient and further research is needed.

Hypoxia-inducible factor (HIF) −1α

HIF-1α serves as a well-known glycolytic regulator, which is mainly regulated by hypoxia. Upon stimulation, HIF-1α translocates into the nucleus to form a heterodimer, binding to hypoxia-response element (HRE) sequence and targeting glycolytic enzymes as mentioned above [16].

Evidence has proven that HIF-1α played predominant roles in MSC immunomodulation and metabolism. In addition to hypoxia stimulation, R. Contreras-Lopez et al discovered that TNF-α and IFN-γ primed MSCs exhibited a significant increase of HIF-1α expression and nuclear translocation and enhanced therapeutic effects in DTH. They further confirmed that after silencing HIF-1α of MSCs, the inhibitory capacities on Th1 and Th17 cells and the secretion of immunomodulatory factors were significantly diminished, which was also related to the metabolic alteration from glycolysis to OXPHOS [10]. Overexpression of HIF-1α of human dental mesenchymal stromal/stem cells inhibited dendritic cell differentiation and promoted monocytes toward immunosuppressive types with reduced TNF-α and increased IL-10 production [27]. In consistent with this, HIF-1α overexpression also promoted MSC extracellular vesicles (EVs) secretion and immunosuppressive factors (IDO, COX2 and PD-L1) expression. Furthermore, EVs derived from HIF-1α overexpressed MSCs presented better therapeutic effects on DTH murine models, with M1 macrophages decreasing and M2 macrophages increasing [28]. Mechanically, the increased secretion of exosomes in MSCs induced by HIF-1α was attributed to the activation of notch ligand Jagged-1, which was also involved in the regulation of immune cells [29,30]. Interestingly, a dramatical increase of HIF-1α expression induced by tridimensional (3D) compaction of MSCs [31], which will be discussed below, could contribute to enhanced immunoregulation of MSCs [32]. Taken together, HIF-1α overexpression or induced by hypoxia, inflammation or 3D culture promotes a metabolic shift towards glycolysis and enhances immunomodulatory properties in MSCs.

Inflammatory cytokines enhance immune functions through glycolysis

Interferons (IFNs)

IFNs are polypeptides produced by infected cells, regulating the host antimicrobial defense and orchestrating the immune responses [33]. As well investigated, priming MSCs with IFN notably increased immune functions by inducing IDO, which is an initial rate-limiting enzyme of tryptophan catabolism and a critical immune-regulatory factor in MSCs [34]. Naive MSCs expressed undetectable IDO unless they were induced by IFN-γ and the catabolic activity of this enzyme licensed MSC immunoregulatory effects [1]. The tryptophan depletion and kynurenine (the product of tryptophan by IDO) increase contributed to the immunomodulation of MSCs, especially on T cell suppression [35].

Recently, IFN-enhanced immunomodulatory abilities of MSCs have been reported to be associated with glycolytic metabolism. As shown in a proteomic and metabolomic experiment, MSCs primed with IFN-γ exhibited elevated expression of the glycolytic enzyme (GLUT5 and HK2) and enhanced immune regulatory factors such as IDO, TGF-β, antigen-presenting proteins, and chemokines [36]. The IFN-γ-primed MSCs notably attenuated the symptoms of GVHD and improved survival in the mouse model. To further investigate the signaling pathway, Y. Liu et al discovered that IFN-γ exposure led to ECAR increase but mitochondrial electron transport activity decrease, indicating that the metabolic state of MSCs shifted from OXPHOS to glycolysis [11]. Mechanically, they claimed that IFN-γ activated AKT/mTOR signaling pathway, which was crucial in metabolic reconfiguration from OXPHOS to glycolysis, boosted the IDO and PGE2 expression in MSCs and consequently suppressed T cell proliferation [11]. Besides, another study described that IFN-β induced rapid signal transducer and activator of transcription 1 (STAT1) and STAT3 activation in MSCs and upregulated its downstream hepatocyte growth factor (HGF) expression, mediating T-cell proliferation inhibition. This regulatory process was associated with IFN-β stimulated-mTOR signaling, facilitating glycolytic capacity and concomitantly promoting immune function of MSCs, which might be the mechanism of the experimental autoimmune encephalomyelitis (EAE) treatment [37].

Interleukin-1 (IL-1)

IL-1 is mainly produced by immune cells such as macrophages, neutrophils, dendritic cells and NK cells, which is involved in pro-inflammatory and immunomodulatory actions. As an inflammatory stimulus, unequivocal evidence has shown that pretreatment with IL-1 endowed MSCs with increased immunomodulatory and anti-inflammatory capacities, improving the treatment outcomes. For example, the precondition of IL-1 alone or combined with other inflammatory stimuli increased the production of immunomodulatory factors (IDO-1 and PGE2) or exosomes secretion, enhancing MSC immunomodulatory and anti-inflammatory capacities in osteoarthritis and septic [38–41].

Besides immune-regulation, IL-1 has been reported to target the glycolytic process by stimulating glucose uptake or activating glycolytic enzyme, which was reviewed elsewhere [42]. For example, both IL-1α and IL-1β were identified to enhance the glucose uptake in different cells, including rheumatoid synovial cells [43], human gingival fibroblasts [44], astrocytic brain cells and human chondrocytes [45]. A recent study discovered that IL-1β enhanced glycolysis in lung adenocarcinoma cells [46]. In contrast, blockage of IL-1 signaling pathway inhibited glycolysis in Th17 cells, alleviating GVHD severity [47]. Mechanically, evidence showed that IL-1β-dependent signal was associated with PI3K/AKT/mTOR signaling pathway [48], which was a regulatory pathway in glycolysis (discussed above). As for stem cells, research has discovered that priming with β-glucan, a prototypical trained-immunity-inducing agonist, induced immune effects of hematopoietic stem cells (HSCs) through enhancing glycolysis, which was mediated by IL-1β [49]. Collectively, given that IL-1 could regulate glycolysis in various cells and IL-1 could enhance MSC immunomodulatory properties, it is possible that IL-1 regulates MSC immunometabolism through glycolysis.

Tumor necrosis factor-α (TNF-α)

Another inflammatory cytokine TNF-α has been widely discussed in the activation of MSC immunomodulation [50] since it was believed to supply the initial stimulus for MSC priming [51]. TNF-α precondition strengthened a plethora of immunomodulatory factors expression of MSCs, including IDO, PGE2, IL-6 [52,53], NO [54] and exosomes secretion [55], enhancing MSC therapeutic efficiency in colitis and rheumatoid arthritis [52,56].

Interestingly, these TNF-α-triggering immunomodulation of MSCs could be affected by glycolysis, since recently, studies have reported that TNF-α participated in the regulation of glycolysis. For instance, TNF-α could induce metabolism toward glycolysis, with the increment of HIF-1α and GLUT1 expression through TNF/TAK1/HIF-1α/glycolysis signaling axis [57]. Furthermore, A. H. Remels et al demonstrated that TNF-α activated the NF-κB pathway, promoted HIF-1α activation and thus elevated glycolytic metabolism [58]. Similarly, as discovered by Q. Xu et al, exogenous TNF-α or endogenous TNF-α produced by LPS-stimulated macrophages promoted glycolysis and lactate secretion in human lung fibroblast cells [59]. Besides glycolytic regulation, TNF-α could also

participate in tryptophan metabolism since it induced IDO in MSCs, however, more evidence should be added.

Environmental factors promote glycolytic metabolism

Hypoxia

MSCs reside in a hypoxic niche *in vivo*, preferring to use glycolysis to sustain a quiescent state with low ROS [60]. However, when delivered into a non-physical culture environment *in vitro* or injured sites *in vivo*, MSCs experience "culture shock" which requires metabolic reconfiguration in response to the environmental cues to dictate their immunomodulatory functions. Exposed to hypoxia MSCs exhibited higher immunomodulatory and anti-inflammatory capacities. For example, hypoxia-pretreatment MSCs produced more immune-regulating factors of IDO, PGE2 and PD-L1, exerting enhanced inhibiting effects on $CD4^+/CD8^+$ T lymphocyte proliferation and increasing more regulatory T cells (T-reg) [61–63]. In the humanized mouse model of GVHD, MSCs primed with mild hypoxia (5%) produced more immunomodulatory factors to inhibit T cell proliferation and improved the survival of GVHD compared with naive MSC-injected mice [64]. The underlying mechanism associated with the metabolic pathway was that hypoxia stimulated glycolysis in the MSCs, which promoted immunomodulatory capacities. Hypoxia stabilized HIF-1α, which translocated to the nucleus and enhanced glycolysis in MSCs by activating glycolytic genes or PDKs as mentioned above. Collectively, hypoxia pretreatment promisingly becomes viable strategies of promoting MSC immune-regulatory potentials through the metabolic pathway.

3D culture

3D culture mimics the natural environment where MSCs reside and preserves or even promotes some cellular characteristics, including enhancing the immunomodulatory properties. Several lines of evidence have uncovered that aggregation of MSCs into 3D spheroids promoted the secretion of anti-inflammatory or immunoregulatory factors, strengthened regulation on immune cells and thus elevated MSC therapeutic potentials [65,66]. For example, 3D aggregation of MSCs exhibited enhancing anti-inflammatory regulation on activated macrophages [67]. Similarly, intraluminally injected MSC spheroids downregulated inflammatory cytokines and numbers of macrophages, ameliorating dextran sulphate sodium (DSS)-induced colitis [68]. In another study shown by J.A. Zimmermann et al, spheroidal MSC aggregates combined with microparticle delivery of IFN-γ increased and sustained suppression on T-cell activation and proliferation, which maximized the effects of IFN-γ on MSC immunomodulation [69].

Interestingly, these benefits of 3D aggregation could be attributed to metabolic reconfiguration, which altered mitochondrial morphology, reduced OXPHOS and switched metabolic flux toward glycolysis. As demonstrated by Y. Liu et al, 3D aggregation upregulated glycolytic associated gene expression (HK2, PKM2, and lactate dehydrogenase A (LDHA)) and reduced mitochondrial membrane potential [32]. Mechanically, previous views held that the oxygen restriction in the aggregates resulting in the hypoxic milieu caused the alteration of cellular properties [70,71]. However, studies have shown only a slight reduction of oxygen tension in the 3D aggregates. Instead, metabolic reconfiguration (metabolic shift to glycolysis) of MSCs mainly resulted from size-dependent mechanical compaction, which activated the PI3K pathway [72]. Taken together, the 3D culture alters the morphology, cell to cell contact and external environment of MSCs, which leads to a metabolic shift toward glycolysis and elevates immunomodulatory capacity.

ATP metabolism

ATP supplies energy for cellular biological behaviors, determining cellular functions. The majority of ATP is produced by mitochondrial through respiration and OXPHOS (Fig. 1). Metabolism of ATP including ATP production and hydrolysis regulates MSC immunomodulatory properties [73]. As reported by M. Pasztorek et al, mitochondrial dynamics (including ATP supply) could influence MSC immunomodulatory abilities [74]. Similarly, the serum-free medium significantly induced the ATP release of MSCs, which prevented apoptosis [75]. Interestingly, studies found that the hydrolysis of ATP into adenosine monophosphate (AMP) and adenosine also mediated the immune functions of MSCs. For example, S.S. Jeske et al discovered that MSCs hydrolyzed ATP into adenosine dependent of ectonucleotidases CD39 and CD73 expression, mediating their immunosuppressive properties [76]. Similarly, when MSCs were cocultured with activated T cells, which expressed a high level of CD39, there was a significant increase of adenosine production from ATP compared with T cells or MSCs alone, resulting in the suppression of T cells [77]. In addition to ATP metabolism in MSCs themselves, MSCs could also influence the mitochondrial dynamic and ATP metabolism in immune cells, regulating their functions. As several studies demonstrated that, MSCs transferred mitochondrial to immune cells to modulate their functions by restoring the mitochondrial membrane potential, mitochondrial function and ATP production [73,78], which will be discussed below. Collectively, changes in the cell culture environment or exposure to external stimuli (such as coculturing with activated immune cells) result in ATP metabolic alteration (synthesis and hydrolysis), which further influences the immunomodulation of MSCs.

Lipid metabolism

Lipid metabolism, which is comprised of fatty acid (FA) anabolism and catabolism (especially fatty acid oxidation (FAO)) plays a pivotal role in cell biological behaviors. Fatty acid synthesis (FAS), mediated by fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC) participates in the membrane glycerophospholipids (GPL) formation, which is required for cell division and expansion [79]. On the other hand, FAs serve as energy storage in the form of triglycerides (TAG) in lipid droplets (LDs) and are ready to oxidize in the mitochondria to fuel the Krebs cycles to release ATP. In addition to determining cell proliferation or differentiation, both FAS and FAO significantly affect the immune cell functions, which has been reviewed elsewhere [80,81], suggesting that lipid metabolism can influence the immune capacities.

Studies on MSC-based therapy on metabolic diseases such as type II diabetic diseases and non-alcoholic fatty liver disease discovered that MSCs ameliorated the disease progression through regulation of lipid metabolism [82,83]. With the technique improvement, a lipidomic analysis of MSCs conducted by Campos et al emerged and reported that after pro-inflammatory stimulation, the lipid molecular profile of MSCs significantly changed, with the phosphatidylcholine (PC) species with shorter fatty acids (FAs) decreasing and lysoPC (LPC 18:0) levels increasing. Simultaneously, the levels of phosphatidylethanolamine (PE), phosphatidylserine (PS) and sphingomyelin (SM) in MSCs also dramatically altered compared with the untreated counterpart [84]. These suggested that the immune and anti-inflammatory capacities of MSCs might be associated with lipid metabolism (Fig. 2).

The widely investigated lipid-associated immune-regulation of MSCs was the PGE2, which was a major metabolite produced by a long-chain polyunsaturated fatty acid (arachidonic acid) through

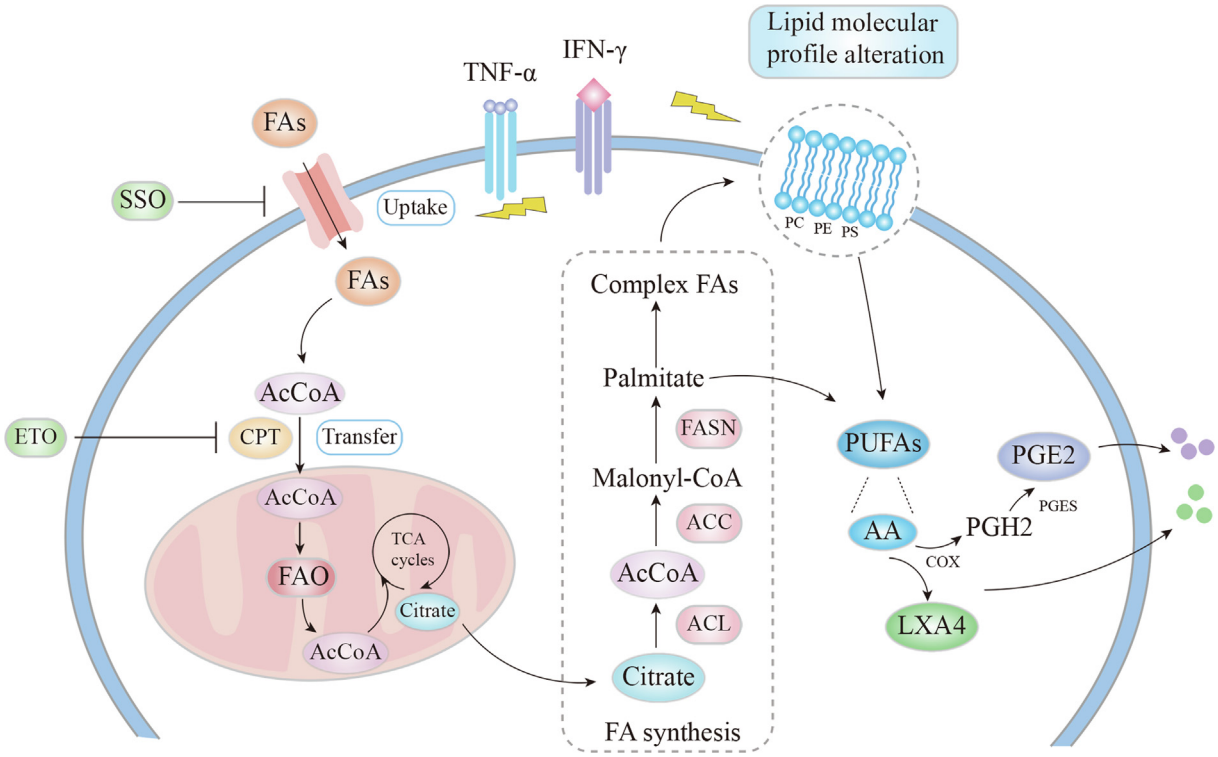

Fig. 2. The lipid metabolism associated immune-regulation in MSCs. Inflammatory stimuli (TNF-α and IFN-γ) can influence the lipid molecular profile and the fatty acid uptake and thus FAO in MSCs. The phospholipids on cell membranes can produce a polyunsaturated fatty acid, AA, which can be catalyzed to PGE2, or LXA4 through COX, both mediating the immunomodulation of MSCs. FAs, Fatty acids; AcCo, acetyl-CoA; CPT, palmitoyltransferase; FAO, fatty acid oxidation; SSO, sulfosuccinimidyl oleate; ETO, etomoxir; PUFAs, polyunsaturated fatty acids; AA, arachidonic acid; COX, cyclooxygenase; LXA4, lipoxin A4; PGH2, Prostaglandin H2; PGES, prostaglandin E synthases; PGE2, prostaglandin E2; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine.

cyclooxygenase (COX) catalyzation [85]. Indeed, PGE2 was recognized as a key factor secreted by MSCs when exposed to various populations of immune cells including T cells, NK cells, DCs and macrophages and it mediated MSC immunosuppressive or anti-inflammatory functions through binding to the prostaglandin receptors [86], which had been discussed at large elsewhere [87–91]. Another polyunsaturated fatty acid, lipoxin (LX), also derived from arachidonic acid [92], was demonstrated to be involved in the MSC-based therapy on acute lung injuries. The secretion of lipoxin A4 (LXA4) by MSCs decreased the TNF-α in the lung injury mice models and improved the mice survival, whereas, the therapeutic effects were reversed by the LXA4 receptor antagonist [93]. Moreover, as mentioned above, manipulation of PPARβ/δ in MSCs exerted anti-inflammatory effects in different tissues [94], dictating their immune abilities and therapeutic potential of various diseases. Since PPARβ/δ was a master regulator of FAO, the link between lipid metabolism and MSC immunomodulation seemed to be predictable.

However, there existed a contradictory result. A study performed by R. Jitschin displayed that the lipid metabolism seemed not to affect the MSC immune capacities. They found that primed MSCs with inflammatory cytokines exhibited enhanced FA uptake and increased FAO [95]. Whereas, this increased dependency on FAO after inflammatory stimulation did not result in elevated MSC immunomodulation. The block of the carnitine palmitoyltransferase (CPT), transferring fatty Acyl-CoA to mitochondria for FAO, with etomoxir (ETO) and inhibition of exogenous FA uptake with sulfosuccinimidyl oleate (SSO) did not affect T cell suppression. Moreover, ETO and SSO did not downregulate the expression of immunomodulatory factors (IDO1 and COX2) of MSCs [95].

Taken together, although the lipid metabolism (FAS and FAO) as well as the biologic lipid such as the polyunsaturated fatty acids play a critical role in the immune regulation, the direct evidence that the lipid metabolism mediates MSC immune functions is scant and controversial. More thorough work is required to uncover this interacting link and the underlying mechanism.

Amino acid metabolism

Amino acids are fundamental units, the metabolism of which is essential for MSC proliferation and biologic functions. The emerging evidence reflects that amino acid metabolism plays important roles in the immune regulations of MSCs (Fig. 3).

Arginine metabolism

The metabolic pathways of arginine are divided into two ways: decomposed into urea and ornithine by arginase, which is critical for cell growth and proliferation; Oxidized into biologically active monoxide nitrogen (NO) through nitric oxide synthase (NOS), which participates in various biological regulation. A recent study illustrated that the electrical stimulation promoted the chondrogenesis of ADSCs, partially by upregulation of arginine catabolism, contributing to the enhanced therapy for the cartilage defects [96]. Additionally, arginine affected immunomodulatory functions. For example, T cells required it for activation and one of the mechanisms that MSCs inhibiting T cell proliferation was creating an arginine exhaustion environment through upregulating iNOS [97,98]. Laila Rashed et al demonstrated that the administration of MSCs combined with arginine, which induced NO production, downregulated the apoptosis and inflammation in rats with injured gastric mucosa [99]. In fact, the iNOS-mediated MSC immunomodulation was demonstrated in several research. iNOS-mediated immunosuppression enhanced the secretion of NO in

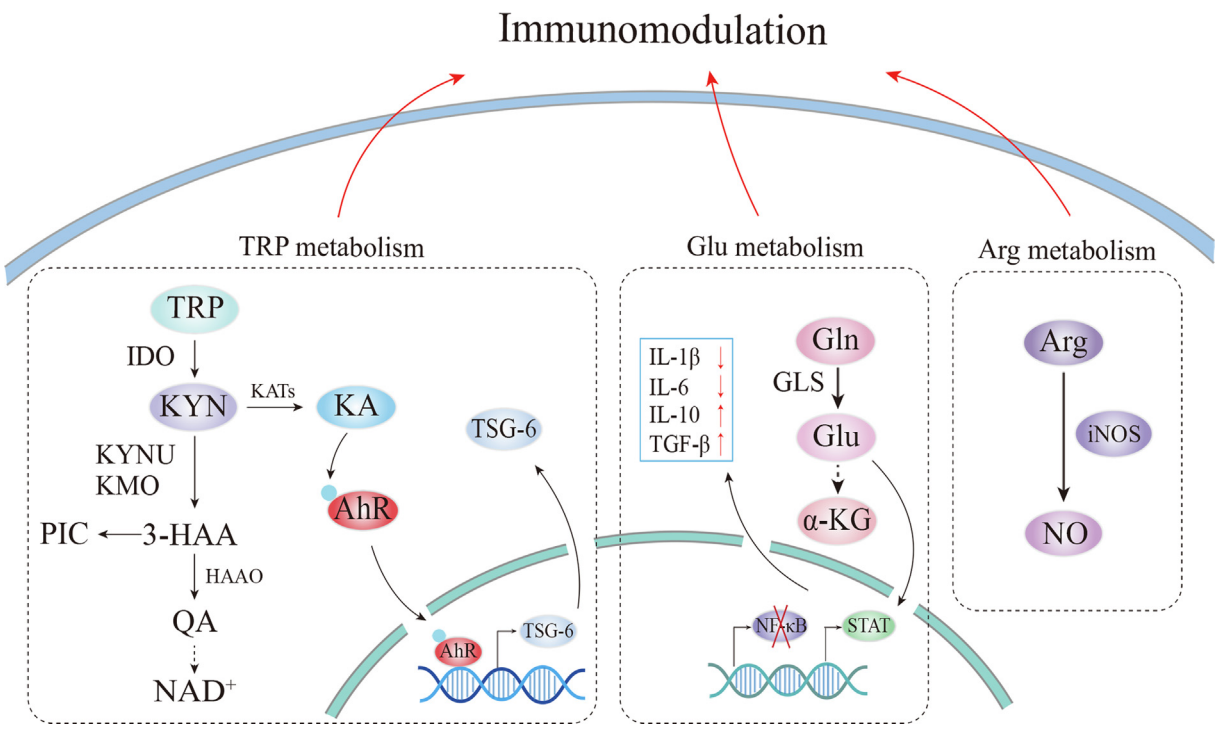

Fig. 3. Amino acid metabolism in MSC immune functions. TRP can be converted into KYN by IDO, which is then further catalyzed into KA through KAT. The TRP depletion and KYN production contribute to immunomodulation. KA is the ligand of the AhR, promoting AhR to enter into the nucleus and directly bind to the TSG-6 promoter. KYN can be also metabolized to 3-HAA and finally produces NAD^+. The intermediates along the pathway have immunomodulatory effects, which have not been demonstrated in MSCs. Moreover, Glu can decrease the IL-1β, IL-6 production and increase IL-10 and TGF-β secretion through activation of STAT and inhibition of NK-κB. Arg can be converted into NO by iNOS, regulating immune cells. TRP, tryptophan; KYN, kynurenine; IDO, indoleamine 2,3-dioxygenase; KA, kynurenic acid; KATs, kynurenine aminotransferases; KYNU, kynureninanse; KMO, kynurenine 3-monooxygenase; 3-HAA, 3-hydroxyanthranilic acid; PIC, picolinic acid; HAAO, 3-hydroxyanthranilate 3,4-dioxygenase; QA, quinolinic acid; Gln, glutamine; Glu, glutamate; GLS, glutaminase; Arg, arginine.

MSCs, inhibiting T lymphocyte proliferation by blocking STAT5 phosphorylation [34,100]. MSCs lack of iNOS exhibited impaired therapeutic effects in acute liver injury and fibrosis [1,101]. Although there was no direct evidence demonstrating that MSCs depended on arginine metabolism to regulate immune functions, this link was possible and promising to construct considering that NOS is involved in arginine catabolism and serves as the immune-regulator of the MSCs.

Glutamine metabolism

Glutamine, albeit an unnecessary amino acid, can be utilized in almost every cell as a substrate to provide the demanding energy and precursors for the synthesis of crucial macromolecules for growth. Besides, glutamine is regarded as an immunonutrient since in infection or high catabolic conditions, the consumption rate of the glutamine in immune cells exceeds the glucose [102], suggesting its critical roles in the immune system. For example, glutamine metabolism is required for lymphocytes proliferation and cytokine production through activation of ERK and JNK kinases, which finally upregulated the transcription of cell proliferation-related genes [102]. In neutrophils, the consumption of glutamine was the highest compared with other immune cells [103], most of which was converted into glutamate. The glutamine metabolism in neutrophils enhanced superoxide production and promoted bacterial killing. As for macrophages, their activation was largely affected by glutamine metabolism. The synthesis and release of pro-inflammatory cytokines in macrophages relied on glutamine availability while the glutamine metabolite α-KG was reported to promote M2 macrophage differentiation [104].

Previous researches reported that BMSCs required glutamine metabolic product α-KG for proliferation, specification, and differentiation. Stimulation of the enzyme glutaminase (Gls), which broke down glutamine to form glutamate and α-KG, enhanced BMSC osteogenesis whereas diminished adipogenesis [105]. The role of glutamine metabolism in regulating MSC immune functions was discovered by G.G. Dos Santos, demonstrating that treatment with glutamate downregulated IL-1β and IL-6 production while upregulated immune factors (TGF-β, IL-10) in BMSCs through NF-κB inhibition and STAT-3 activation [106]. Moreover, the addition of glutamine in the BMSC conditional medium decreased the pro-inflammatory factors and increased the anti-inflammatory cytokine of lymphocytes and macrophages. Collectively, the glutamine metabolism of MSCs can become a novel target to dictate MSC immune capacities and the further mechanism is worthy of studying.

Tryptophan-kynurenine metabolism

The essential amino acid tryptophan is mainly catabolized by the kynurenine pathway (KP), of which kynurenine (KYN) is the first stable metabolite mediated by IDO or tryptophan 2,3-dioxygenase (TDO). Subsequently, during the metabolic process, several other intermediates are generated, including 3-hydroxyanthranilic acid (3-HAA), quinolinic acid (QUIN), kynurenic acid (KA) and picolinic acid (PIC).

The metabolic activity of IDO, which participated in the activation of the kynurenine pathway, has been widely investigated as a potential mechanism of the MSC immunosuppressive effect on the immune cells. Meisel et al demonstrated that IFN-γ induced IDO expression in MSCs in a dose-dependent manner. The primed MSCs

showed increased IDO activity and enhanced immunosuppressive capacities, especially inhibition of T cell proliferation [107–109], which was widely investigated in immune and inflammatory diseases such as GVHD [110], EAE [111] and CCl4-induced liver injury [112]. Moreover, the application of competitive inhibitors of IDO, such as 1-methyl-tryptophan (1-MT) rescued the inhibition effects of MSCs on immune cells, including T cells [108]. *In vivo*, IDO also mediated MSC immune function and therapy effects. As validated in the murine model of EAE, MSC-treated mice presented the greater expression of IDO in the spleens and showed greater recovery, which was not observed in the 1-MT treatment mice [113]. Besides adaptive immune cells, S. Lee et al claimed that the upregulated IDO of MSCs converted innate immune cells, macrophages, from pro-inflammatory M1 to anti-inflammatory M2 subsets and limited inflammatory cytokines secretion [114].

In addition to tryptophan depletion, following the induction of IDO expression, tryptophan was further broken down into variant and immune-active metabolites. The initial stable product was KYN, which was elaborately investigated for its immunomodulatory roles in T cells, natural killer cells (NKT) [115], dendritic cells (DC) [116], monocytes [117], and macrophages. For example, KYN suppressed $CD4^+$ and $CD8^+$ T cell proliferation in a dose manner through binding to the Aryl hydrocarbon receptor (AhR) [118]. Furthermore, L.F. Campesato et al uncovered that KYN promoted Tregs generation, resulting in M2-like macrophage expansion. The IDO-KYN-AhR-mediated immunosuppression was modulated by crosstalk between Tregs and tumor-associated macrophages [119]. Likewise, also acted as the AhR agonist, KA, which was transformed from KYN by kynurenine aminotransferases (KATs), had a similar immune regulation. G. Wang et al discovered the immunosuppressive effect on T cells of MSCs was attributed to IDO mediated TSG-6 upregulation and more specifically, to its metabolite KA [2]. As illustrated in the chromatin immunoprecipitation, KA activated AhR and enhanced its direct bind to TSG-6 promoter, which exerted immune function in the acute liver injury (ALI) mice model. This promotion of TSG-6 was reversed through knocking down KATs, preventing the KA production [2]. Moreover, KA was described to have anti-inflammatory capacities in several mental diseases [120,121], inflammatory bowel disease [122] and atherosclerotic disease [123]. Through the PPARδ-HO-1 pathway, KA ameliorated LPS-induced inflammatory response in macrophages, reducing the TNF-α and IL-6 secretion [124]. Mechanically, KA bound to GPR35, which was widely expressed in the immune cells and mediated its immune regulation.

On the other way, KYN was catalyzed by kynurenine 3-monooxygenase (KMO) and kynureninanse (KYNU) into 3-HAA, which was also reported to exert immune regulatory effects. For example, 3-HAA modulated the immune system by inhibiting T cell growth and reducing macrophage-mediated inflammation [125]. In atherosclerosis, 3-HAA could disturb inflammasome activation and IL-1β production in macrophages. In this context, targeted inhibition of HAAO, which prevented 3-HAA from breaking down and endogenously increased the level of 3-HAA, attenuated hypercholesterolemia and atherosclerosis [126].

The final product NAD^+ was essential in the immune cell energy metabolism. A recent study revealed that the KYN-derived NAD^+ influenced energy metabolism by maintaining mitochondrial respiration in macrophages, which mediated their anti-inflammatory and phagocytic capability.

However, the evidence of these metabolites in the kynurenine pathway mediating the MSC immune functions is little, which needs to be further demonstrated. If so, the utilization of agonist or antagonist or combinations of the different enzymes in the tryptophan-kynurenine metabolism of MSCs turns out to be a promising avenue to regulate immune functions and enhance therapeutic potentials.

Other amino acids

Studies showed that amino acids could tune the functions of immune cells by diverse mechanisms [127]. For example, serine, leucine and valine influenced the energy metabolism (glycolysis and OXPHOS); Cysteine, glutamine, and glycine maintained the intracellular redox balance and thus regulated the ROS production; The intermediates of methionine, arginine, glutamine, the leucine, valine and isoleucine affected the post-translational modifications (PTMs) of proteins. However, whether these amino acids are involved in MSC immune function is as yet unknown and more amino acids remained to be uncovered.

MSCs regulate immune cell metabolism

The emerging evidence has shown that metabolism in immune cells predicts and dictates their fate and function. Their functional alteration depends on the metabolic switch from quiescent to an activated state, shunting nutrients into distinct directions to instruct the appropriate immune polarization. For instance, a metabolic shift towards aerobic glycolysis was required for T cell activation, which provided sufficient substrates for the production of lipids, proteins, nucleic acids, and other carbohydrates. After stimulation, DCs underwent a metabolic switch to aerobic glycolysis [128]. As for macrophages, the distinct arginine metabolism defined the two types of the cell, with the pro-inflammatory M1 subsets utilizing it through iNOS, while M2 macrophages through arginase1 [129]. Moreover, M2 macrophage differentiation heavily relied on OXPHOS, notably FAO, to fuel their long-term function. Consistently, induction of PPARβ/δ, the upstream of FAO, promoted alternatively activated macrophages through STAT6 and suppressed inflammation [130,131].

MSCs regulate immune cell metabolism

Recent studies show that MSCs exert their immune-regulation and therapeutic effects through triggering the metabolic alteration in immune cells. For example, L. Pan et al displayed that the therapeutic effects of human umbilical cord Wharton's jelly-derived MSCs (hWJ-MSCs) on fulminant hepatitis relied on the metabolic regulation of T cells. Specifically, hWJ-MSCs inhibited T cell activation and proliferation by blunting the glycolytic pathway [132]. Consistently, M. Bottcher et al reported that MSCs mimicked the effects of mTOR inhibitor, blunting the glycolysis in T cells and therefore suppressing T cell activation, which could be mediated by IDO metabolic activity [133]. Furthermore, EVs derived from MSCs were incorporated by lymphocytes, suppressing T cell proliferation and Th1 differentiation concomitant with promoting Treg cell differentiation. M. Bottcher further demonstrated that the glycolytic enzyme, PKM2 expression and mitochondria membrane potential decreased in MSC-EV-priming T cells, suggesting metabolic regulation in T cells [134]. Another study focused on the macrophage metabolism indicated that the conditioned medium from the murine ADSCs promoted AKT/mTOR pathway activation and upregulated PPARγ expression and lipid droplet biogenesis in M2 macrophages, which mediated their therapy in experimental colitis and sepsis [135]. Likewise, when cocultured with macrophages, MSCs skewed metabolism of macrophages to M2-like bioenergetic state, with decreasing glycolysis while increasing CPT1α expression, a key enzyme for FAO (mentioned above). Meanwhile, the metabolic signaling factor, p-mTOR was also significantly reduced by MSCs both in M1 and M2 macrophages [136]. In the ALI mice model, MSCs administration profoundly transformed the metabolomic profile of the liver-resident immune cells and remarkably ameliorated liver damage. In their high-

performance chemical isotope labeling liquid chromatography-mass spectrometry (CIL LC-MS) experiment, three major metabolic pathways (arginine, glutamate and aspartate metabolism) exhibited the most affected, suggesting that MSC therapeutic potential might be attributed to disturbing these metabolic pathways in immune cells in ALI [137]. MSCs administration reversed the level of citrulline and ornithine in untreated ALI, priming the immune cells to shunting arginine into arginase (Arg) 1 hydrolysis and mitigating ALI severity. Similarly, MSCs reduced the pro-inflammatory factors (IL-6, TNF-α) by altering the metabolites in the cecal ligation and puncture (CLP) induced lung and liver injury in septic rat models and thus improved the survival rates [138].

Metabolic regulation through mitochondria transfer

Interestingly, one possible mechanism of the metabolic regulation might be mitochondria transferred from MSCs to immune cells either by direct cell–cell contacts or paracrine secretion within EVs [25]. Of note, mitochondria served as a primary site of OXPHOS and played key roles in energy balance and cell metabolism, the function of which determined the immune cell functions. For example, in the model of acute respiratory distress syndrome (ARDS) and sepsis, macrophages received the mitochondria from MSCs through tunneling nanotubes (TNT)-like structures, increasing OCR and promoting phagocytic capabilities [139]. Since M2 macrophage differentiation heavily relied on OXPHOS, Y. Yuan et al uncovered that MSCs delivered mitochondria to macrophages, decreasing the glycolysis while increasing the basal respiration and thus promoting anti-inflammatory M2 macrophages polarization in diabetic nephropathy mice, which was regulated by PGC-1α/TFEB mediated autophagy [140]. Furthermore, mitochondria trafficking to mouse splenocytes via F-actin nanotubes significantly promoted Treg cells and inhibited effector T cells with increasing OCR and ATP production [141]. In addition to direct-contact delivery, mitochondria could be normally encapsulated in EVs to the immune cells. Following engulfing the EVs derived from BMSCs, which contained mitochondria, alveolar macrophages in an ARDS environment showed enhanced anti-inflammatory functions and phagocytosis. These mitochondria-enriched EVs abrogated inflammation and lung injury *in vivo* [142]. As reported by A.C. Court et al, MSCs delivered mitochondria through EVs mainly to $CD4^+$ cells rather than $CD8^+$ T cells or $CD19^+$ B cells. The artificial transfer of mitochondria promoted $CD4^+$ T cells activation and Treg cell differentiation by upregulating FOXP3, IL2RA, CTLA4, and TGFb1 expression in the GVHD murine model [143]. Mechanically, a recent study discovered that the mitochondria delivered from ADSCs depended on the HLA expression and were associated with HLA-C and HLA-DRB1 eplet mismatch load between ADSC and Treg donors [144]. Furthermore, CD39/CD73 signaling drove the MSC mitochondria trafficking and subsequently stabilize BACH2 and SENP3 to induce Treg cell expression of FOXP3 [145]. Additionally, the mitochondria status of MSCs determined the mitochondrial transfer. The delivery and function of mitochondrial of human synovial MSCs from rheumatoid arthritis patients to Th17 cells reduced compared with healthy BMSCs [146].

In summary, MSCs regulate immune cell functions through metabolic reconfiguration by mitochondria transferring, which improves the mitochondrial respiratory function in immune cells, resulting in immunosuppressive effects.

MSCs in regenerative clinical application

MSC-based cellular therapies have been applied and achieved great results in various clinical settings. ADSCs which are easy to obtain and possess high immunomodulation functions, have been widely applied in regenerative conditions including wound healing and scar repairs [147–149], hair growth [150,151], face rejuvenation [152,153], soft tissue regeneration [154,155] and breast reconstruction [153,156].

Regenerative plastic surgery

In the systematic review and clinical research, the safety and efficacy of ADSCs or stromal vascular fraction (SVF) and fat grafting which contained ADSCs have been confirmed in wound and scar healing and face rejuvenation treatments [148,152]. Additionally, adding platelet-rich plasma (PRP), a high-concentration platelet-oriented plasma, containing abundant nutritional and growth factors, could significantly enhance the fat grafting survival [157] and regenerative effects of ADSCs [158], which promoted proliferation and multiple differentiation of ADSCs [159]. Similar regenerative results could be seen in soft tissue reconstruction, using fat graft with ADSCs or PRP [154,155,160]. Mechanically, in addition to secreting various growth factors or pro-angiogenic factors, the regenerative abilities of ADSCs could also be attributed to immunomodulatory and anti-inflammatory effects. The potent immunomodulatory properties of ADSCs was promoting macrophage phenotype from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype, which was crucial for wound and scar repairs [161,162].

Hair regrowth

Autologous micrografts enriched with human hair follicle mesenchymal stromal/stem cells (HF-MSCs) or ADSCs exerted favorable outcomes with an increase of hair count and hair density [150,151]. Similarly, PRP could exert nearly equal effects as HF-MSCs or clinical drugs in hair regrowth [163,164]. Since androgenic alopecia (AGA) could trigger an inflammatory and immune response, the anti-inflammatory and immunomodulatory properties of PRP or HF-MSCs or ADSCs could be one of the important mechanisms for AGA treatment and hair regrowth [150,165].

A new application of ADSCs in coronavirus disease 2019 (COVID-19)

Recently, MSC-based therapy on COVID-19 pneumonia achieved satisfying results through immunomodulation [166]. The applied MSCs included dental pulp stromal/stem cells, umbilical cord stromal/stem cells, mesenchymal stromal/stem cells and ADSCs [167]. Compared with drugs and vaccines, ADSC treatment on patients with COVID-19 showed satisfying results attributed to potent immune-regulatory and antiviral effects of ADSCs [168].

Taken together, these regenerative effects of MSCs in the clinical application might be associated with metabolism, which needs more evidence to explore.

Conclusion and future perspectives

The metabolism has emerged as a central hub influencing MSC biological functions and therapeutic potentials. In this review, we discuss the metabolic-mediated MSC modulation on the immune cells and their therapeutic effects. Therefore, metabolism manipulation provides a promising target to enhance the MSC therapeutic efficiency (Table 1). Although, the evidence is clear that the enhancement of glycolysis of MSCs contributes to their immunomodulatory improvement and thus promotes the therapeutic effects, the exact mechanism of how this metabolism affects the immune functions of MSCs is still under exploration. More specific signal pathways which are associated with glycolysis in MSCs and subsequently result in their immune regulations require

Table 1
Direct evidence of MSC-based therapy for disease models associated with immunometabolism.

Animal models of diseases or injury	Associated metabolism	Findings	Year	MSC source	Reference
Delayed-type hypersensitivity (DTH) murine model	Shift from glycolysis to OXPHOX	HIF knocking down exhibiting reduced inhibition on Th1 and Th17 and limited potential of Treg production; reducing intercellular adhesion molecule (ICAM), IL-6, and nitric oxide (NO); imparing therapeutic effects on mice syndrome and decreased Treg cells production	2020	Murine MSC isolated from BW	[10]
DTH in mice	Glycolysis	Enhanced immunosuppresion on Th1 and Th17 proliferation and elevated PD-L1, PGE2 Production; alleviating mice syndrome and reducing number of Th1 and Th17 by AMPK pathway	2021	Murine MSC and human MSC	[12]
Cecal ligation and puncture (CLP) sepsis in mice	PGE2	Improving the survial of mice; decreasing TNF-α and IL-6 concentrations; increasing IL-10 from macrophages	2009	Murine BM-MSCs	[90]
Graft-versus-host disease (GvHD) in mice	PGE2	Improving the survival of mice with GVHD; decreaseing IFNγ and TNFα and inhibiting T-cell expansion;	2015	Human bone marrow-derived (BM) MSCs	[87]
Ischemia-reperfusion acute kidney injury (IRI-AKI) in mice	PGE2	IL-17A pretreated MSCs improved the symptom of mice with IRI-AKI through PGE2 secretion; decreased serum IL-6, TNF-α, and IFN-γ levels, a higher serum IL-10 level, and higher spleen and kidney Treg percentages	2018	Murine BM- MSCs	[88]
DSS-induced colitis in mice	PGE2	Inhibiting T cell proliferation and activation; reducing IL-6, TNF-α, IL-17a; increasing the number of regulatory T cells and IL10, TGF-β; skewing macrophages into the anti-inflammatory M2 phenotype;	2019	Human ADSCs	[89]
Inflammatory bowel disease (IBD) in mice	PGE2	Reducing inflammatory responses, promoting the functional and structural recovery of colitis; inducing M2 macrophage polarization	2020;	Human placenta-derived MSCs (hP-MSCs)	[91]
LPS-induced acute lung injury (ALI) in mice	Lipoxin A4	Improving the survial of ALI mice partly by secrtion of LXA4; increasing the LXA4 level in BAL fluid of ALI mice and decresing the TNF-α and MIP-2.	2015	Human MSCs	[93]
Experimental autoimmune encephalomyelitis (EAE) in mice	Tryptophan-kynurenines	A significant reduction in Th1 and Th17 lymphocytes; increasing IL-27 and cyp1a1 expression and presence of IL-10-secreting T CD4 + cells.	2021	Murine endometrial-derived MSCs	[111]
ALI mice models	Kynurenic acid, the metabolite of tryptophan catabolism	Acvation of TSG-6; reducing neutrophil infiltration in ALI	2017	Human umbilical cord-derived MSC (hUC-MSC)	[2]
Indomethacin-induced gastric ulcer (GU) in rats	L-arginine	MSC combined with arginine decreasing caspase-3, BAX genes expression and PGE2 and TNF-α serum levels in the gastric ulcer rats; increasing Bcl-2 and eNOS gene expression	2016	Rat BM-MSCs	[99]

to be further explored. On the other hand, given the profound effect of the metabolic intermediates on the immune cells, further studies are required to explore whether these metabolites derived from MSCs exert similar effects on the immune system and how they mediate the immune regulation of MSCs. Notably, the metabolites regulating the functions of immune cells through epigenetic modifications seem to provide a new sight in the MSC therapy, which however, requires more evidence.

Previous investigations focus on glucose metabolism. The recent emerging studies have revealed that the lipid and amino acid metabolism in MSCs are of equal importance to dictate the immune functions. However, the direct evidence is scant and must be further uncovered. Since the metabolism is interactional and not independent, the full understanding of the complex metabolism-mediated immune functions in MSCs is challenging and needs more effort. Besides the metabolic regulation in MSCs itself, MSCs also influence the metabolism in immune cells to exert their therapeutic functions. Interestingly, the mitochondria delivered from MSCs to immune cells influence the cell energy metabolism and thus regulate immune functions, turning out to be a striking mechanism of immunometabolism in MSCs. Collectively, metabolism influences the immune functions of MSCs. The metabolic regulation provides a new avenue for MSC therapy, although more work needs to be done.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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