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The signaling pathways and therapeutic potential of itaconate to alleviate inflammation and oxidative stress in inflammatory diseases

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ABSTRACT

Endogenous small molecules are metabolic regulators of cell function. Itaconate is a key molecule that accumulates in cells when the Krebs cycle is disrupted. Itaconate is derived from *cis*-aconitate decarboxylation by *cis*-aconitate decarboxylase (ACOD1) in the mitochondrial matrix and is also known as immune-responsive gene 1 (IRG1). Studies have demonstrated that itaconate plays an important role in regulating signal transduction and posttranslational modification through its immunoregulatory activities. Itaconate is also an important bridge among metabolism, inflammation, oxidative stress, and the immune response. This review summarizes the structural characteristics and classical pathways of itaconate, its derivatives, and the compounds that release itaconate. Here, the mechanisms of itaconate action, including its transcriptional regulation of ATF3/IκBζ axis and type I IFN, its protein modification regulation of KEAP1, inflammasome, JAK1/STAT6 pathway, TET2, and TFEB, and succinate dehydrogenase and glycolytic enzyme metabolic action, are presented. Moreover, the roles of itaconate in diseases related to inflammation and oxidative stress induced by autoimmune responses, viruses, sepsis and IRI are discussed in this review. We hope that the information provided in this review will help increase the understanding of cellular immune metabolism and improve the clinical treatment of diseases related to inflammation and oxidative stress.

1. Introduction

The tricarboxylic acid (TCA) cycle is the most common metabolic pathway in aerobic organisms [1]. The TCA cycle produces not only adenosine triphosphate (ATP) but also a variety of intermediate metabolites such as citrate, fumarate, α-ketoglutarate (α-KG), and succinate [2]; these intermediate metabolites play significant roles in regulating the immune system by affecting various signaling pathways. In lipopolysaccharide (LPS)-activated macrophages, endogenous immunosuppressants, such as succinate, fumarate, and itaconate accumulate, exert a series of immunomodulatory effects in the body [3–6]. In recent years, metabolites such as itaconate have increasingly attracted the attention of scientists. Their anti-inflammatory roles have been demonstrated in immune cells. We summarize the structural characteristics and classical pathways of itaconate and describe itaconate derivatives and the compounds that release itaconate. Moreover, we explain the mechanisms involved in its activity, including its regulatory effects on the activating transcription factor 3 (ATF3)/inhibitor of nuclear factor kappa B zeta (IκBζ) axis and type I interferon (IFN) transcription; protein modification regulation of Kelch-like ECH-associated protein 1 (KEAP1), inflammasome, Janus kinase 1 (JAK1)/signal transducer and activator of transcription 6 (STAT6) pathway, and tet methylcytosine dioxygenase 2 (TET2); and metabolic regulation of succinate dehydrogenase (SDH) and glycolytic enzymes. Finally, we expound on the roles itaconate plays in inflammatory diseases induced by autoimmune responses, viruses, sepsis, IRI, and oxidative stresses. We expect that the information provided in this review will aid in improving the clinical treatment of inflammatory diseases.

2. Discovery of itaconate

In 1836, Samuel Baup first discovered a by-product of distilled citric acid [7], which was later named itaconate by Crasso GL [8]. In 1932, a filamentous fungus was identified that produced itaconic acid by Kinoshita [9]. In 1945, Kene's laboratory established the first industrial itaconic acid production process in the United States [10]. For a long

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time after the discovery of itaconate, scientists believed that itaconate, in contrast to succinic acid and malic acid, did not play a significant role in mammalian cell metabolism; therefore, itaconate was mainly used in the synthesis of industrial polymers [11,12].

Gradually, however, scientists recognized that itaconate effectively suppressed the growth of a variety of bacteria by inhibiting the activity of isocitrate lyase (ICL) in the context of glucose deficiency [13–15]. In the absence of citrate lyase, itaconate was shown to suppress the growth of bacteria by inhibiting the activity of propionyl-coenzyme A (CoA) carboxylase (PCC) [16]. Studies revealed that itaconate inhibited the replication of Zika virus (ZIKV) in the neural system by inhibiting the activity of SDH during infection [17]. Further exploration indicated that itaconate exerted significant anti-inflammatory effects. In 2011, Strelko et al. demonstrated that LPS or IFN-γ stimulation led to the mass production of itaconate in macrophages [18]. Two years later, Michelucci et al. found that aconitate decarboxylase 1 (ACOD1) encoded by immune-responsive gene 1 (*IRG1*), produced itaconate by catalysing the decarboxylation of aconitic acid, an intermediate product of the TCA cycle [13]. The enzyme had been previously purified, and certain properties were detected by Dwiarti in 2002 [19]. In 2016, Lampropoulou et al. knocked out the IRG1 gene in mice and found that bone marrow-derived macrophages (BMDMs) from these *IRG1*$^{-/-}$ mice exhibited increased production of proinflammatory cytokines after stimulation [20], and the regulatory properties of itaconate on anti-inflammatory cytokines were gradually discovered. Subsequently, two landmark studies published in Nature revealed the mechanism of itaconate action in regulating inflammatory cytokines and immune responses [6,21], which expanded the horizon of research and increased the understanding of the biological effects exerted by itaconate. Given that rewiring macrophage metabolism is crucial for regulating macrophage activities, these two studies extend the understanding of itaconate in regulating macrophage metabolism via the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway and Nrf2-independent ATF3 pathway. Two related research highlights were published in Nature Reviews Immunology to comment on the two studies [22,23]. Fig. 1 shows the timeline of itaconate milestone discoveries (Fig. 1).

3. Metabolic pathways of itaconate and modulation of IRG1

Mitochondria are called “cell powerhouses” because they play an important role in providing metabolic energy for the whole body and maintaining calcium homeostasis [24,25]. The TCA cycle converts acetyl- CoA to CO_2 and harvests electrons for the electronic transport chain, which involves a series of enzyme-catalyzed reactions to produce ATP in the mitochondrial matrix [2]. Itaconate is a metabolite produced when the TCA cycle is bypassed during energy production. *Cis*-aconitate decarboxylase (CAD), which is also known as IRG1 or ACOD1, catalyzes the conversion of *cis*-aconitate to itaconate [13] (Fig. 2). The down-regulation of isocitrate dehydrogenase in M1 macrophages leads to the accumulation of citrate and isocitrate [26]. Through ^{13}C labeling, scientists discovered that glucose-derived carbon flux was redirected to the production of itaconate from that of α-KG in M1 macrophages [27].

Endogenous itaconate is produced in the mitochondria; however, research on the transportation of itaconate across membranes has thus far proven inconclusive. A previous study reported that itaconate was negligibly detectable in M0 macrophages, but its level increased to millimolar concentrations in activated macrophages [13,20]. Meiser J et al. demonstrated that when activated with 10 ng/ml LPS, the average extracellular concentration of itaconate was 9 μM in RAW264.7 cells and 5 μM in BMDMs. The average net release rate for RAW264.7 cells was 2.34 fmol/cell/h, and for BMDMs, was 0.53 fmol/cell/h. The differences in release rates aligned with the intracellular itaconate concentrations (8 mM in RAW264.7 cells and 1.5 mM in BMDMs, respectively) [28]. In addition, exogenous unmodified itaconate markedly increased intracellular itaconate levels in macrophages [29]. Thus, passive diffusion is believed to occur, but further investigation is needed. Itaconate generated by IRG1 in the mitochondrial matrix is predominantly transported across the mitochondrial inner membrane by the 2-oxoglutarate carrier (OGC) [6,29]. Endogenous OGC knockout in RAW264.7 cells resulted in significantly decreased cytosolic itaconate concentration upon LPS stimulation, indicating that the maintenance of the cytosolic itaconate pool hinges on the transportation of itaconate from mitochondria [29].

Itaconate can be degraded by succinyl-CoA synthetase, which produces itaconyl-CoA. Then itaconyl-CoA is hydrated to form (S)-citramalyl-CoA, which is subsequently involved in the production of acetyl-CoA and pyruvic acid [30,31].

Under normal conditions, baseline IRG1 levels are very low [32]. Identifying methods to modulate the expression of IRG1 and generate itaconate is an important area of research. Upon stimulation with LPS, LTA, BoNT/A, CpG-DNA, poly I:C, or KMRC011, the expression of IRG1 increases significantly [33–36]. The expression of IRG1 was modulated by TLR2, TLR4, and TLR9 and was blocked when TLR2 or TLR4 was depleted in activated immune cells [37,38]. Moreover, the expression of IRG1 was elevated when TLR4 was overexpressed in macrophages [39]. Myeloid Differentiation Primary Response Gene 88 (Myd88) encodes a cytosolic adapter protein that plays a central role in the innate and adaptive immune response and functions as an essential signal transducer in the interleukin-1 and Toll-like receptor signaling pathways [40]. Hoshino K et al. demonstrated that TLR4 signaling induced IRG1 gene expression in MyD88-dependent and Myd88-independent pathways, and TLR9 induced IRG1 in a MyD88-dependent manner [34]. In addition, in MyD88$^{-/-}$ cells, some signaling pathways, such as interferon regulatory factor 3 (IRF3), interferon-alpha receptor (IFNAR), and signal transducer and activator of transcription (STATs), induce IRG1 expression [38,41]. In the context of pathogen infection, the production of IFN I and II induces the expression of IRG1 [14,42]; however, the loss of IFNAR inhibits inducible IRG1 expression during pathogen infections [6,14,41]. Shi et al. found that STAT1 deficiency reduced the expression

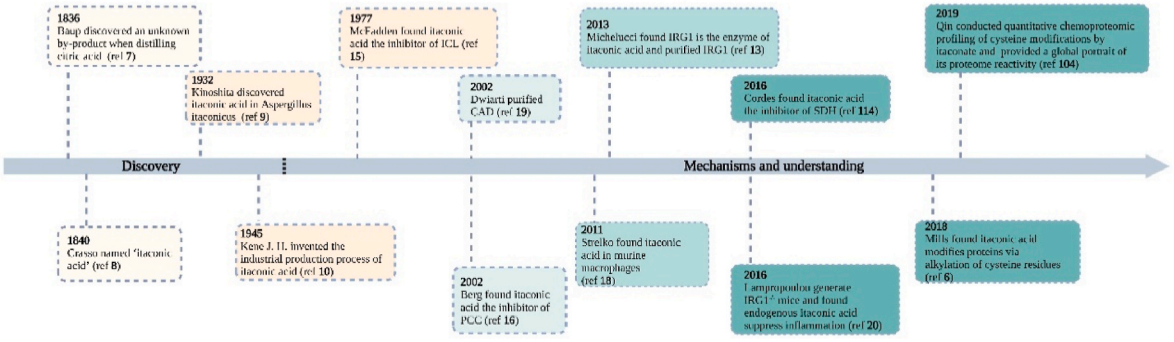

Fig. 1. Timeline of itaconate milestones. The timeline is divided into two parts based on the main studies on itaconate. The first part shows the discovery of itaconate, and the second part depicts the exploration of its mechanisms of action.

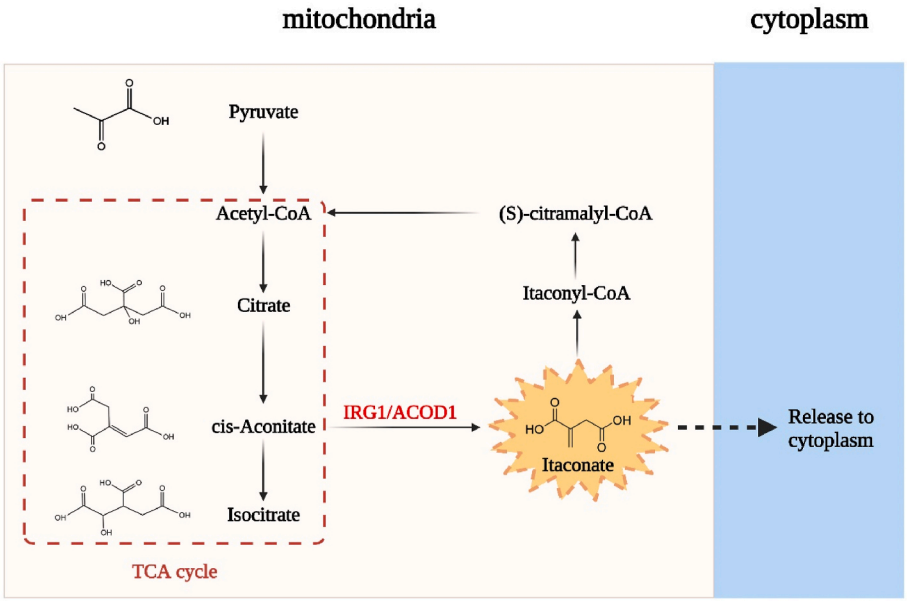

Fig. 2. Metabolism of itaconate. Itaconate is a metabolite produced when the TCA cycle is bypassed during energy production, and IRG1/ACOD1 transforms *cis*-aconitate to itaconate in the mitochondrial matrix. Itaconate is converted to itaconate-CoA and is ultimately catalyzed to form acetyl-CoA, which re-enters the TCA cycle. The process in brown rectangle is part of TCA cycle. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

of IRG1 induced by Mycobacterium tuberculosis (Mtb) infection [41]. In addition to transcriptional regulation, direct and indirect post-transcriptional mechanisms affect the regulation of IRG1. Shi et al. reported that miR-378 directly targets IRG1 and reduces its expression in human glioma cells [43]. Protein kinase C (PKC) regulates protein activity by phosphorylating hydroxyl groups in serine/threonine chains. In the regulation of IRG1, PKC phosphorylates certain unidentified substrates to regulate IRG1 expression. When H7 and genistein were used as PKC inhibitors, the mRNA expression of IRG1 was significantly blocked in RAW264.7 cells [33,44] (Fig. 3).

In addition to IRG1, the key enzyme in itaconate synthesis, pyruvate dehydrogenase (PDH), catalyzes the conversion of pyruvate to citric

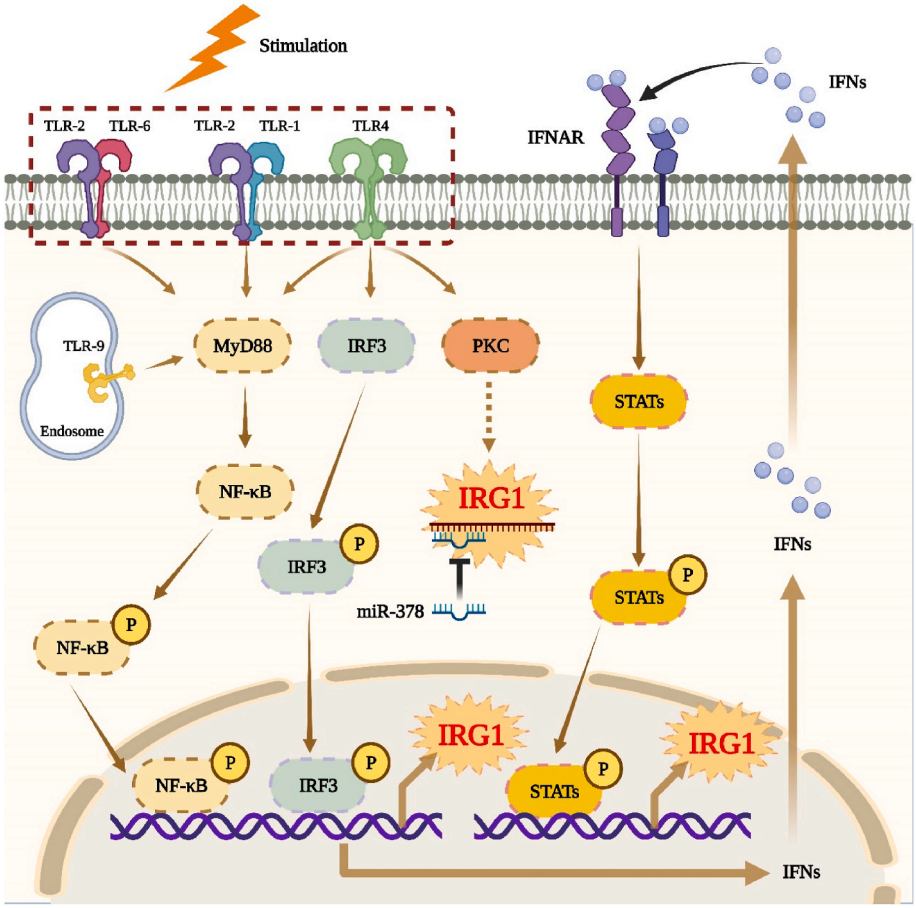

Fig. 3. Modulation of IRG1. Many stimuli can induce the expression of IRG1 by activating certain receptors.

acid. After stimulation with LPS, the activity of pyruvate dehydrogenase kinases 1 (PDK1) is inhibited, and the generation of citric acid is increased, thus increasing the production of itaconate [45,46]. Then, itaconate is catabolized into itaconyl-CoA and subsequently citramalyl-CoA in vivo. Citrate lyase subunit beta-like (CLYBL) protein cleaves citramalyl-CoA to generate pyruvate and acetyl-CoA, which re-entered the TCA cycle in LPS-stimulated RAW 264.7 cells [47].

4. Itaconate and its derivatives

Itaconate is a highly polar α, β-unsaturated dicarboxylic acid with a double bond and two carboxyl groups. Given its chemical structure, itaconate forms a bond with a nucleophile, establishing its chemical properties [48]. Itaconate modifies cysteine residues in proteins via Michael addition reaction, affecting the functions of substrate proteins. Given the chemical composition of itaconate, transportation of exogenous itaconate may be limited across cell membranes into the cytoplasm. Thus, researchers have synthesized a variety of itaconate derivatives, such as dimethyl itaconate (DI), 4-octyl itaconate (4-OI), and 4-ethyl itaconate (4-EI), to illustrate the effects of itaconate. In addition, itaCORMs, a mixture of itaconate and carbon monoxide releasing molecules, and certain biomaterials based on itaconate as a raw material have also been used to explore the potential anti-inflammatory effects of itaconate (Fig. 4).

Scientists esterified the carboxyl group at the 1-position of itaconate to form dimethyl itaconate (DI) and found that the conjugation effect of the ester group prevented electron transfer, reduced the negative charge of itaconate, and enhanced its reactivity in the Michael addition reaction [20]. Studies have shown that DI exerts effects similar to those of dimethyl fumarate (DMF) in vivo by activating Nrf2 and its downstream genes [49]. DI alleviated the LPS-induced inflammatory response by reducing the expression of IκBζ [21]. However, some scientists have argued that the extensive metabolic effects of DI are not caused by its conversion to itaconate but by its electrophilicity and covalent modification; therefore, they contend that DI is not a suitable derivative [50,51]. Subsequently, Mills et al. designed 4-octyl itaconate (4-OI), an itaconate derivative with an ester group located at the distal end of an olefin, which reduced mercaptan reactivity [6]. When compared with the effect of DI, 4-OI simulated the biological effect of itaconate because it increased the level of itaconate via hydrolysis in vivo [50]. The structure of 4-ethyl itaconate (4-EI) is similar to that of DI, but 4-EI shows lower electrophilicity and higher polarity. To the best of our knowledge, only one study has described the biological effects of 4-EI to date [50]; therefore, more studies are required to explore its specific anti-inflammatory mechanism.

Interdisciplinary studies have led to the development of a compound (ItaCORMs) that can release itaconate and CO simultaneously and thus shows better anti-inflammatory effects than itaconate or CO in LPS-stimulated BMDMs [52]. In addition, some scientists started using itaconate as a biomaterial to produce an anti-inflammatory effect. For example, itaconate has been used to coat demineralized bone matrix scaffolds to generate integrated scaffolds that participate in bone repair [53]. In addition, they used itaconate to prepare PCL nanofibres and implanted the nanofibres into mice to maintain the inflammatory response in damaged areas through their proinflammatory effects in the early stage. The nanofibres repair the tissue damage in the late stage to reduce the infarct area after myocardial infarction (MI) [54]. Similarly, scientists have synthesized itaconate as injectable hydrogels to form optimized microenvironments for cardiac stromal cells to promote MI heart repair [55]. Recently, some researchers directly integrated itaconate into a polymer, thus retaining the biological activity of the compound, and found that an itaconate polyester effectively limited the duration and intensity of inflammation compared with the effect of silica gel [56]. All these studies shed new light on the potential use of itaconate in future disease treatments.

5. Roles for itaconate in regulating the inflammatory immune response and oxidative stress

Itaconate has drawn scientists' attention because of its immunoregulatory properties. Scientists mainly use itaconate and its derivatives (exogenous itaconate), *IRG1*$^{-/-}$ macrophages, or *IRG1*$^{-/-}$ mice

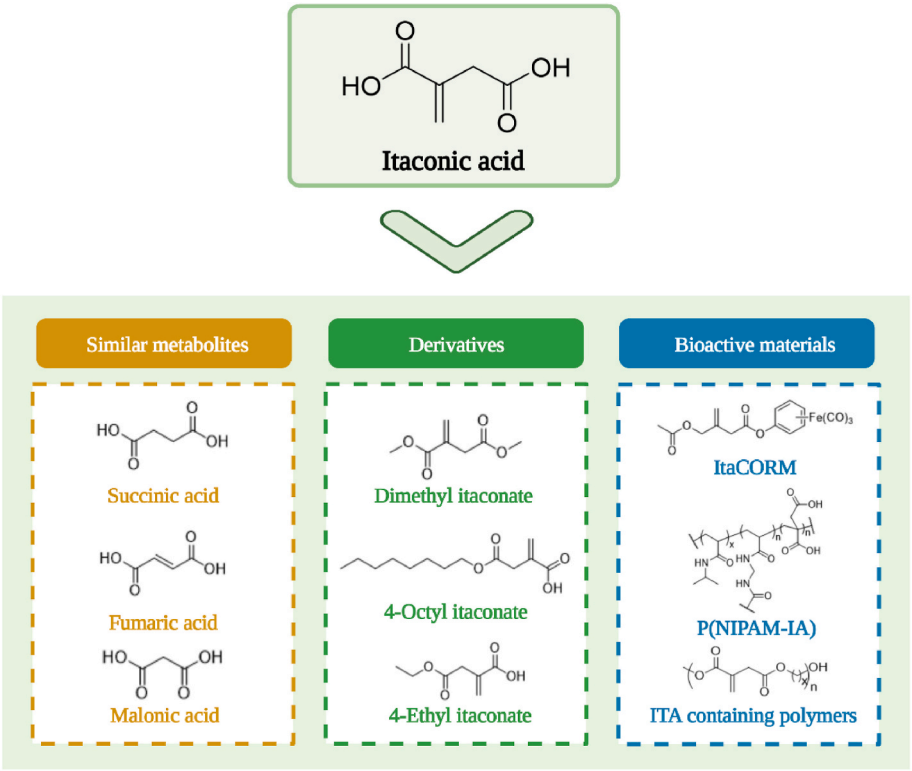

Fig. 4. The structure of itaconate, similar metabolites, derivatives and bioactive materials. Itaconate is structurally similar to certain other metabolites, such as succinate, fumarate, and malonate, which exhibit similar biological functions given their similar structures. Researchers synthesized derivatives of itaconate to leverage their high membrane permeability. Since the rapid development of interdisciplinary studies, ItaCORM, P(NIPAM-IA), and ITA containing polymers have been synthesized to generate anti-inflammatory effects.

(endogenous itaconate) to study the anti-inflammatory mechanisms of itaconate in vitro and in vivo. Because of the unsaturated double bond in itaconate, the cysteine residues in proteins can be covalently modified by itaconate via Michael addition reaction, influencing the activities and functions of proteins [21,50]. Specifically, itaconate regulates inflammatory immune responses and oxidative stress mainly via the following aspects (Figs. 5 and 6).

5.1. Transcriptional regulation

5.1.1. Regulating ATF3/IκBζ axis activity

IκBζ is a nuclear protein with an ankyrin repeat sequence encoded by the nuclear factor (NF)-κB inhibitor zeta (Nfκbiζ) gene [57]. ATF3 is considered an immunomodulatory inhibitor and a key regulator of IFN I activity and its regulatory effect on IFN I is Nrf2-independent [58]. Studies have demonstrated that ATF3 knockout increases the expression of IκBζ and proinflammatory cytokines in mouse embryonic fibroblasts. Moreover, itaconate and its derivatives inhibited IκBζ by upregulating ATF3 and inhibiting the production of the proinflammatory factor interleukin (IL)-6 [59].

Studies have demonstrated that early after LPS stimulation, DI failed to inhibit primary transcriptional responses to LPS, but DI downregulated secondary transcriptional responses in LPS tolerized BMDMs. In regard to *IRG1*$^{-/-}$ mice tolerized BMDMs, the second treatment of LPS increases IκBζ expression compared with wild-type BMDMs [21]. This finding indicates that endogenous itaconate regulates IκBζ. What's more, scientists generated DI conjugated with glutathione via its electrophilic properties, and the conjugate leads to a decrease of reactive oxygen species (ROS)[21]. Therefore, itaconate and its derivatives suppress the inflammatory response by regulating the ATF3/IκBζ pathway.

5.1.2. Regulation of type I IFNs

Activated macrophages secrete a large number of I IFNs and play important roles in the inflammatory response [60]. Notably, type I IFNs exert multiple effects to reduce infections [61]. Swain et al. found that itaconate and its derivatives played different roles in the regulation of type I IFNs. DI and 4-OI effectively inhibited the expression of type I IFNs in LPS-stimulated macrophages [6,21], while the level of type I IFNs increased significantly after pretreatment with unmodified itaconate [50]. These results indicate that itaconate and its derivatives played different roles in regulating type I IFNs. The production of type I IFNs was reduced in *IRG1*$^{-/-}$ macrophages in an endogenous itaconate deficiency model, but this decreasing trend was effectively reversed after unmodified itaconate treatment, indicating that itaconate enhances the expression level of type I IFNs in vivo [50]. In addition, 4-OI reduced the expression of stimulator of interferon genes (STING)-dependent type I IFNs by activating Nrf2 [62], but the exact mechanism remains unclear and needs to be elucidated in future studies.

5.2. Protein modification regulation

5.2.1. Regulating KEAP1 activity

KEAP1 is a substrate recognition subunit of the E3 ubiquitin ligase that mediates the degradation of Nrf2 [63]. In the context of oxidative stress and inflammation, the KEAP1-Nrf2 complex is disassociated, and Nrf2 is translocated to cell nuclei, where it regulates the antioxidant response element (ARE) to drive the expression of ARE-dependent genes and the gene encoding various detoxifying enzymes [64,65]. Studies have demonstrated that DI and 4-OI play effective roles in antioxidation

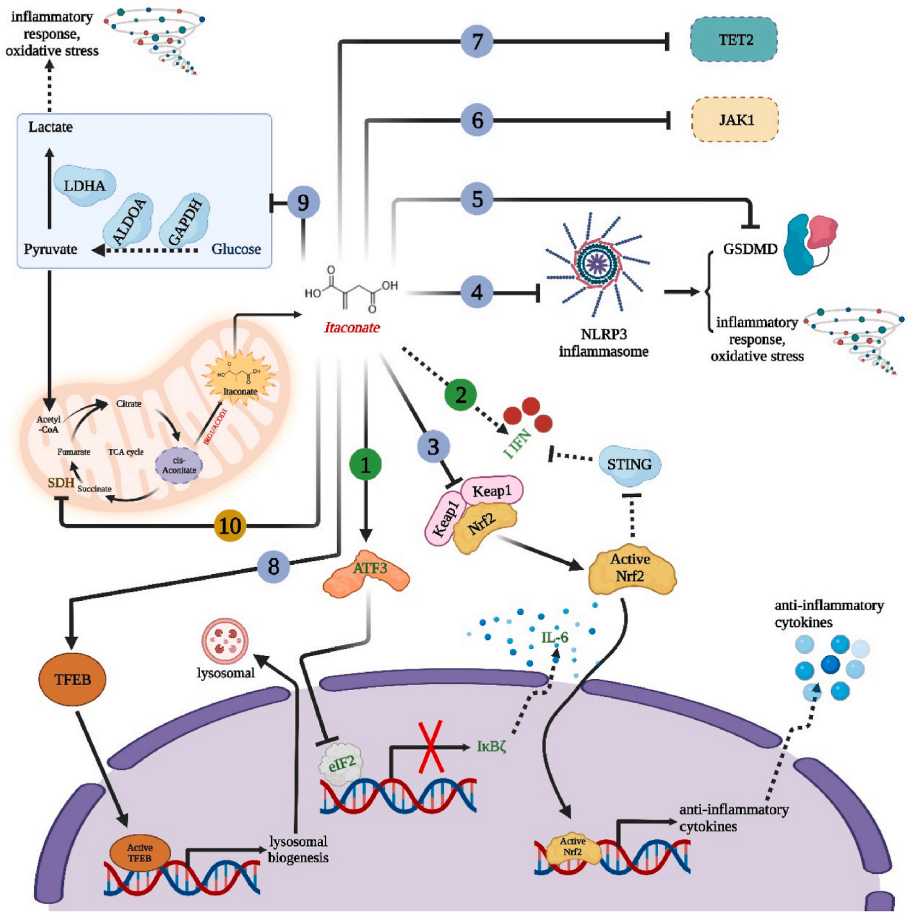

Fig. 5. The classical signaling pathways by which itaconate regulates the inflammatory response and oxidative stress. These classical signaling pathways by which itaconate regulates the inflammatory response and oxidative stress can be divided into three types: (1) transcriptional regulation, including the regulation of the ATF3/IκBζ axis, and type I IFN activation (① & ②); (2) protein modification regulation, including the regulation of the KEAP1, inflammasome, JAK1-STAT6 pathway, TET2 catalytic activity, and TFEB nuclear translocation (the specific methods of modification are shown in Fig. 6, ③-⑨); and (3) metabolic regulation, including inhibition of the activity of key glycolytic enzymes and SDH (⑨ & ⑩).

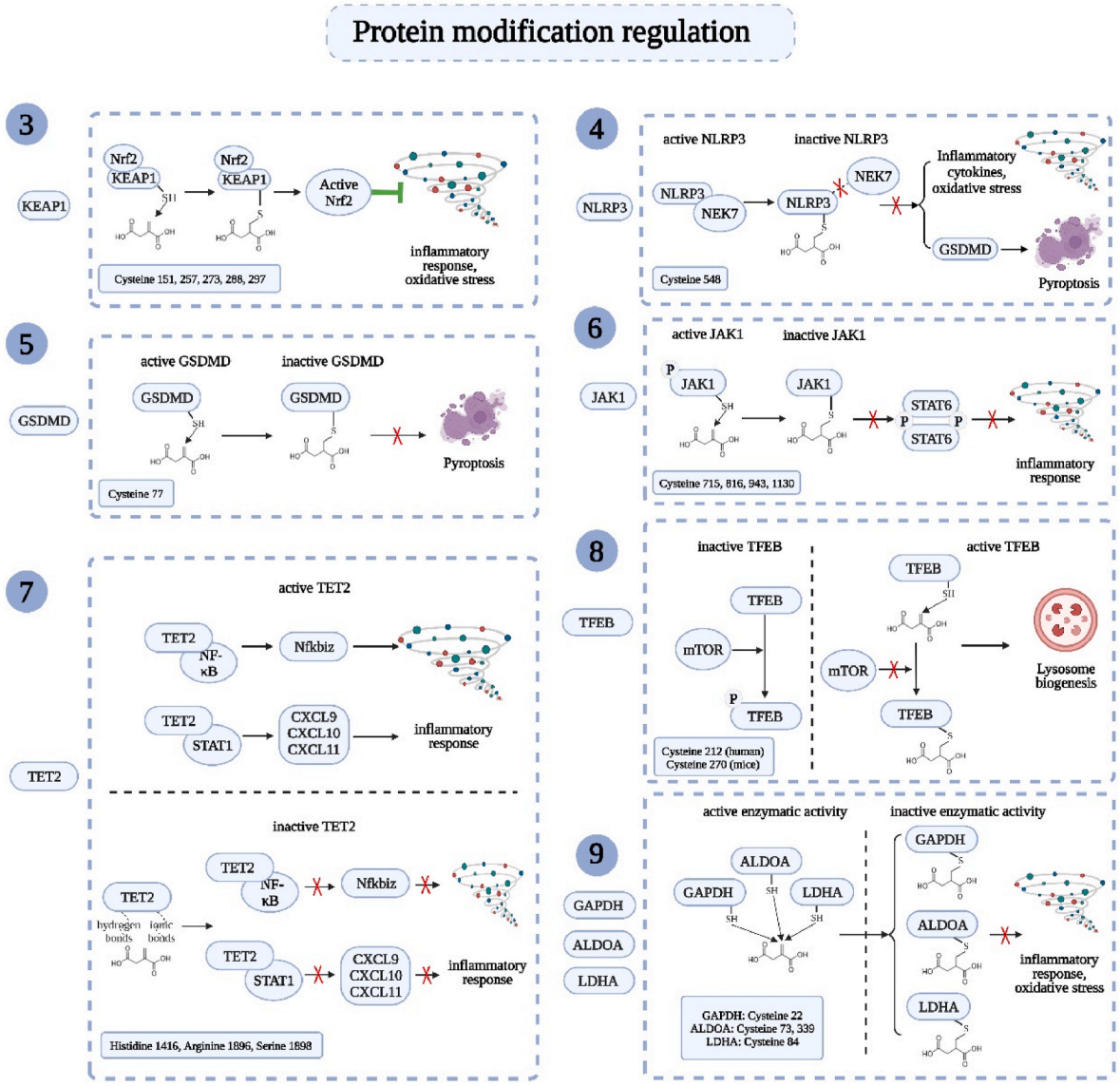

Fig. 6. Itaconate and its derivates modify proteins to regulate the inflammatory response and oxidative stress. The numbers in each box correspond to the numbers in Fig. 5. This figure shows detailed descriptions of the roles played by itaconate and its derivatives in protein modification regulation.

by activating Nrf2 and inactivating NF-κB [66–70]. Because it is an a, β-unsaturated dicarboxylic acid with a mild electrophilic effect, itaconate has been used by scientists to modify the cysteine residue of KEAP1 through Michael addition reaction to inhibit the activity of KEAP1 and prevent Nrf2 degradation. Moreover, 4-OI modified cysteine residues 151, 257, 273, 288, and 297 (C151, C257, C273, C288, C297) in KEAP1 [6]. KEAP1 was also modified with unmodified itaconate and demonstrated anti-inflammatory and antioxidant roles effects in LPS-stimulated macrophages, suggesting that exogenous and endogenous itaconates play the same roles in regulating the KEAP1/Nrf2 pathway [71]. In addition, LPS stimulation of Nrf2 was effectively inhibited in *IRG1*$^{-/-}$ macrophages [6,72]. However, scientists extracted macrophages from *IRG1*$^{-/-}$ mice stimulated with particulate matter (PM) and found that IRG1/endogenous itaconate did not aggravate PM-induced inflammation or Nrf2 activation in macrophages [73]. Therefore, these researchers suggested that 4-OI did not play the same role as endogenous itaconate. Overall, most studies have demonstrated that itaconate and its derivatives play a significant protective role in anti-inflammatory and antioxidant responses by modifying the cysteine residues of KEAP1 to inhibit KEAP1 activity and activate Nrf2 via LPS stimulation.

5.2.2. *Regulating inflammasome activity*

Activation of the inflammasome is an important signature of inflammatory diseases [74]. Inhibiting inflammasome activation is an effective treatment for inflammatory diseases [75]. Lampropoulou et al. found that when stimulated with LPS and ATP, IL-1β and IL-18 expression was significantly decreased in *IRG1*$^{-/-}$ BMDMs [20]. Swain et al. also demonstrated that itaconate exerted a significant effect on inhibiting IL-1β expression in a transcription-independent manner [50]. Based on these findings, the inhibitory effect of itaconate on inflammasome activation is most likely mediated through its direct regulation of NLRP3. Hooftman et al. found that 4-OI prevented NLRP3 from binding to NEK7 by modifying the cysteine 548 (C548) residue of NLRP3 and reducing the expression of IL-1β, and these effects were SDH- and Nrf2-independent [76]. Gasdermin D (GSDMD) is an important downstream molecule of NLRP3 and an executor of pyroptosis. In 2015, three teams reported the regulatory effects of GSDMD on pyroptosis [77–79]. Since this discovery, GSDMD has become an important molecule in inflammatory responses and inflammatory diseases. Performing proteomic analyses, Bambuskova et al. demonstrated that itaconate prevented caspase-1 activation and GSDMD processing after long-term LPS priming via modification of the cysteine 77 (C77) residue by endogenous

itaconate [80]. Although GSDMD is a molecule involved in the NLRP3-caspase-1 axis, inflammasome activation may depend on GSDMD activity during late inflammasome activation. Intensive research and the development of drugs targeting the NLRP3 inflammasome are currently underway. As an inhibitor of NLRP3, MCC950 was once considered a candidate drug for the treatment of arthritis [81], but it failed to yield the expected effects in clinical trials. As the adverse effects of endogenous metabolites are relatively mild compared with those of synthetic drugs, itaconate is expected to become an inhibitor of inflammasome activity and used for the treatment of inflammation-related diseases.

5.2.3. Regulating JAK1-STAT6 pathway activity

In asthma, pulmonary anaphylaxis, and pulmonary fibrosis, M2 macrophages and T helper 2 (Th2) cells acquire characteristics consistent with a type 2 inflammatory response [82], suggesting that M2 macrophages may play a pathological role in certain diseases. The JAK-STAT pathway plays important roles in inflammatory diseases and regulate macrophage activation [83]. Runtsch et al. found that both itaconate and 4-OI directly modified the four cysteine residues C715, C816, C943, and C1130 in JAK1 and inhibited JAK1 and STAT6 phosphorylation. Finally, itaconate and 4-OI inhibited macrophage M2 polarization and alleviated diseases caused by macrophage M2 polarization mediated via JAK1 modification [84].

5.2.4. Regulation of the catalytic activity of TET2

α-KG is a key metabolic intermediate in the TCA cycle. Some studies have reported that α-KG is a key cosubstrate of TET2 and can form hydrogen and ionic bonds with H1416, R1896, and S1898 in TET2 [85]. In addition, TET2 regulates immune cell differentiation, homeostasis, and function [86–91]. Based on this evidence, Chen et al. found that itaconate inhibited TET2 activity by directly binding to TET2 in a manner similar to the mechanism of α-KG action. The inhibition of NF-κB-TET2 and STAT1-TET2 may explain why many proinflammatory genes in the NF-κB pathway and STAT1 pathway are inhibited by itaconate in LPS-induced macrophages, yielding an anti-inflammatory effect [92].

5.2.5. Regulation of TFEB

TFEB is the key transcription factor of lysosomal biogenesis [93]. When TFEB is phosphorylated by mTOR at serine residue S211, it binds with 14-3-3 regulatory proteins and resides in the cytoplasm. When TFEB phosphorylation is disrupted, TFEB is translocated into the nucleus, where it regulates the transcription of lysosome- and autophagy-related genes [94]. Zhang et al. found that 4-OI modified TFEB at Cys212, disrupted the phosphorylation of TFEB, and induced TFEB nuclear translocation. In addition, nuclear TFEB facilitated lysosomal biogenesis and cleared bacteria during the innate immune responses [95].

5.3. Metabolic regulation

5.3.1. Targeting key glycolytic enzymes and inhibiting glycolysis

Based on alterations in immunophenotypes, the states of energy metabolism in macrophages undergo significant changes. During an inflammatory response in macrophages, the glycolytic metabolic rate increases, and the oxidative phosphorylation rate decreases [3,96–99]. In addition, under oxidative stress, cells utilize glycolysis to generate large amounts of lactate [100–102]. In this process, the interaction between LDHA and NADH leads to the release of electrons, which are transferred into the mitochondrial electron transport chain and transformed into ROS [103]. Therefore, the determination of whether itaconate promotes the anti-inflammatory and antioxidant phenotype acquisition of macrophages by inhibiting glycolysis has become a popular research direction. Recent studies have shown that the anti-inflammatory and antioxidant effects of itaconate and its derivatives can be achieved by regulating aerobic glycolysis [104–106]. Qin et al. developed a specific thiol-reactive probe to detect the quantitative chemoproteomic profiling of cysteine modifications mediated by itaconate and found that 260 proteins, including some key glycolytic enzymes, such as ALDOA and LDHA, were modified by itaconate. Itaconate modified the cysteine residues (C73 and C339) of ALDOA and the cysteine residue (C84) of LDHA to reduce their catalytic activity. In addition, intracellular glucose consumption and lactate production rates were reduced by these modifications, and ALDOA activity was significantly increased in *IRG1*$^{-/-}$ cells [104]. Liao et al. found that 4-OI directly alkylated the cysteine residue (C22) of GAPDH, inhibited its enzymatic activity, and reduced lactic acid production and extracellular acidification rates. When the cysteine residue (C22) of GAPDH was replaced with an alanine residue, IL-1β production was reduced significantly [105]. The anti-inflammatory effect of itaconate was consistent with the effect of heptelidic acid, a specific inhibitor of GAPDH, indicating that itaconate played an important role in inhibiting glycolysis and the inflammatory response by targeting GAPDH.

5.3.2. Inhibition of SDH activity

SDH is not only a key metabolic enzyme in the TCA cycle, which converts succinate into fumarate, but is also a significant component of mitochondrial respiratory chain complex II [107–112]. SDH oxidizes accumulated succinate to form reduced coenzyme Q and returns electrons to mitochondrial respiratory chain complex I to produce ROS [113]. Given that itaconate and succinate are both located in the same part of the mitochondrial matrix and share similar structures, itaconate competes with succinate to prevent succinate from oxidizing into fumarate by binding at an active site of SDH [20,114] and inhibits the production of mitochondrial ROS (mtROS) driven by mitochondrial respiratory chain complex I by inhibiting the activity of SDH, thus effectively suppressing the inflammatory response [115,116]. In LPS-stimulated *IRG1*$^{-/-}$ BMDMs, the succinate level was decreased, whereas the oxygen consumption rate was increased significantly, suggesting that itaconate is an effective inhibitor of SDH [114].

6. Roles of itaconate in inflammatory and oxidative stress-induced diseases

Itaconate is involved in many diseases related to inflammation and oxidative stress. In this review, we describe the roles of itaconate in the following diseases: autoimmune disease-induced inflammation, virus-induced inflammation, sepsis, ischaemia-reperfusion injury, and oxidative stress-induced diseases (Fig. 7).

6.1. Impact on autoimmune disease-induced inflammation

Autoimmune diseases constitute a group of inflammatory conditions that usually affect joints, muscles, bones, tendons, and ligaments and sometimes affect other organs of the body [117]. These diseases affect approximately 5% of the population worldwide [118–120]. More than 200 autoimmune diseases, including systemic lupus erythematosus (SLE), multiple sclerosis (MS), psoriasis, rheumatoid arthritis (RA), and cryopyrin-associated periodic syndrome (CAPS), have been described. Many autoimmune diseases are progressive and affect patients' quality of life. A key focus of research involves the identification of methods to repair an unbalanced immune system that destroys tissues in autoimmune diseases.

The treatments for autoimmune diseases are mainly focused on conventional immune suppression and often lead to serious side effects, including infections and malignancies [121–123]. Itaconate and its derivatives have been demonstrated potential efficacy in the treatment for multiple autoimmune diseases, such as SLE, MS, psoriasis, RA, and CAPS. Scientists have used metabolomics to discern the metabolic spectrum of SLE and RA patients and animal models. Li et al. found that itaconate expression was markedly decreased in the blood samples of

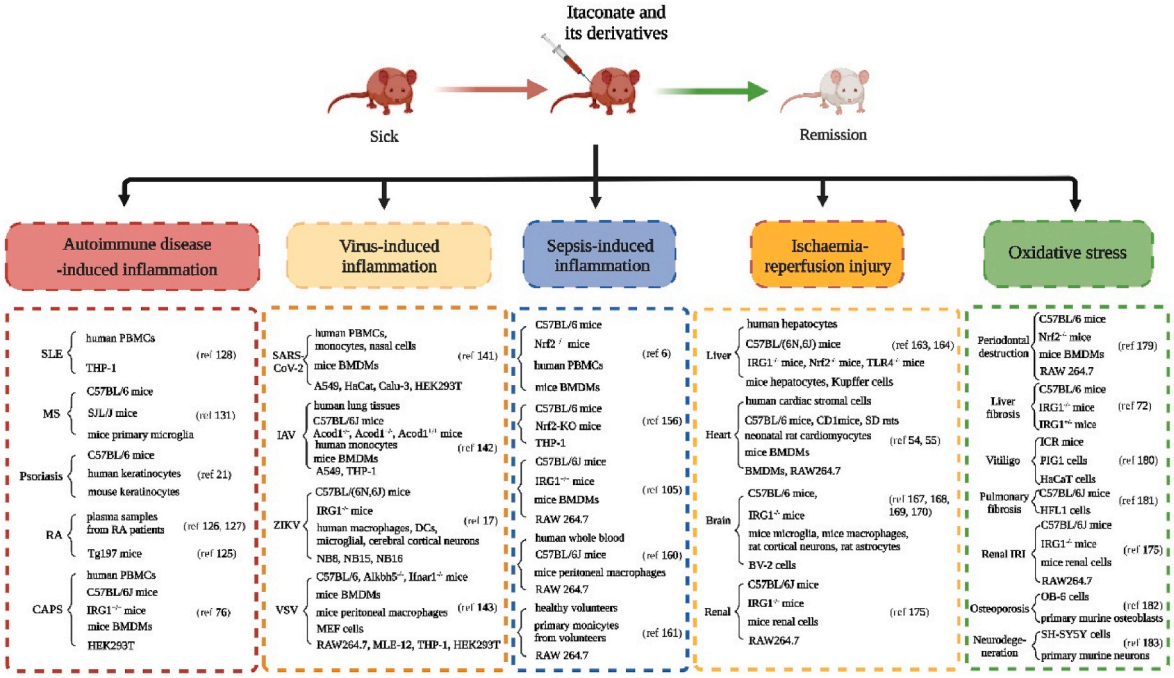

Fig. 7. The roles of itaconate in different inflammatory and oxidative stress-induced diseases and the animal and cell models used in these cited studies. Itaconate plays a significant role in many inflammatory and oxidative stress-induced diseases, and the references cited in this review are presented in the table after the listing of the related disease.

SLE patients [124]. By analysing serum, urine, and synovial fibroblasts at different stages of RA development, Michopoulos et al. found that itaconate was strongly associated with disease progression and could be used as a disease marker for RA [125]. Similarly, two teams from the UK and the USA published studies on the changes in plasma metabolite levels in RA patients on the journal of Metabolites. Both of these groups found that itaconate played a significant role in the pathogenesis of RA [126,127].

In addition to their roles as disease markers, itaconate and its derivatives represent potential treatments for autoimmune diseases. Tang et al. used 4-OI to treat THP-1 cells and PBMCs from SLE patients and found that itaconate inhibited the expression of inflammatory cytokines in the THP-1 cell line and PBMCs obtained from SLE patients by promoting the Nrf2 signaling pathway [128]. 4-OI also effectively inhibits the release of IL-1β in PBMCs isolated from patients with CAPS [76]. Since NLRP3 inhibitors (parthenolide and oridonin) inhibit NLRP3 activation by modifying the cysteine of NLRP3 [129,130], 4-OI may also modify the cysteine residues of NLRP3 to exert a protective effect. DI, another derivate of itaconate, plays an immunosuppressive role in an animal model of experimental autoimmune encephalomyelitis (EAE) by inhibiting matrix metalloproteinase (MMP) 3/9 production, the activation of microglia, the differentiation of Th1/Th17 cells and the infiltration of the central axis nerves [131]. Moreover, DI intervention has been used to alleviate pathological changes in the skin of mice with psoriasis caused by imiquimod (a TLR7/8 agonist) [21]. In *IRG1*$^{-/-}$ mice, the number of IL-17 A-mediated T cells induced by imiquimod was increased significantly [80].

DMF has been approved by the US Food and Drug Administration (FDA) for the treatment of certain autoimmune diseases. Saracino et al. conducted a clinical study using DMF to treat SLE patients and found that the clinical symptoms and quality of life of these patients were significantly improved after treatment with DMF. Moreover, the combination of DMF and other drugs showed no adverse effects in this clinical study [132]. Unni et al. reported that DMF activated Nrf2 by modifying reactive cysteine in KEAP1, and analogues of DMF (fumaric acid and itaconate) showed similar effects [133]. Meanwhile, DMF modified GAPDH to inhibit aerobic glycolysis [134]. As itaconate and its derivatives share a similar molecular structure with DMF, it has been demonstrated to be an effective therapeutic option for certain autoimmune diseases.

6.2. *Impact on virus-induced inflammation*

Itaconate plays a significant role in the inflammatory response induced by viruses. Beginning at the end of 2019, the COVID-19 epidemic is still raging worldwide. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) evades the immune system through a variety of mechanisms and reduce the number of immune cells, especially in the blood and lung [135,136]. Autopsies of patients who died from COVID-19 were performed, and the analyses demonstrated minimal active viral infection but the accumulation of many immune cells in the dead body [137]. The pathological changes caused by COVID-19 are mainly divided into two stages: 1) after infection, rapid viral replication leads to direct virus-mediated tissue damage, and 2) based on the first stage, numerous effector immune cells are recruited, resulting in persistent local and systemic inflammatory responses that remain active even after virus clearance [138]. Therefore, organ failure caused by COVID-19 is mainly a result of excessive activation of the immune system. Liu et al. detected different proteins in the urine samples of 86 COVID-19 patients, 55 pneumonia patients, and 176 healthy controls using a proteomic method. They found that CLYBL, an important enzyme that converts itaconate into acetyl-CoA, was specifically upregulated in COVID-19 patients, especially in patients with severe disease [139]. Their finding is consistent with the previous research showing that decreased itaconate plasma levels in patients with severe COVID-19, as indicated by metabolomics analysis [140]. These results suggest that itaconate plays an important role in treating COVID-19. Olagnier D et al. found that 4-OI directly inhibited the replication of SARS-CoV-2. In addition, 4-OI limited the excessive activation of IFN by regulating the activity of Nrf2, thereby inhibiting the inflammatory response induced by the virus and relieving the clinical symptoms in COVID-19 patients [141]. Similarly, itaconate has demonstrated

antiviral and anti-inflammatory effects on influenza A and ZIKV [17,142].

However, itaconate promotes virus replication during vesicular stomatitis virus (VSV) infection. Studies by the team of Cao Xuetao showed that during VSV infection, host cells impaired the enzymatic activity of the m6A demethylase alkB homolog 5 (ALKBH5) and reduced the mRNA stability and protein expression of α-ketoglutarate dehydrogenase (OGDH) [143]. With reduced OGDH, the production of itaconate was also decreased, and viral replication was inhibited in vivo. However, upon infection with VSV, IRG1 expression resulted in excessive inflammatory cell infiltration and extensive lung damage in vivo [144]. During respiratory syncytial virus (RSV) infection, itaconate contributed to the production of ROS and inflammatory cytokines, resulting in damage to the lung tissue, and *IRG1*$^{-/-}$ mice showed effective inhibition of VSV infection [145].

6.3. Impact on sepsis

Sepsis is considered the most typical medical disorder of this era and is the leading cause of morbidity and mortality in hospitalized patients [146]. Even patients with sepsis who are discharged from the hospital, show a significantly increased risk of rehospitalization and long-term risk of death. Approximately one-half of these patients are hospitalized at least once within a year, and nearly one-sixth of these patients do not survive the first year after discharge [147–149]. Studies have found that during the development of sepsis, pathogens evade protective defense mechanisms, leading to sustained host damage and imbalanced immune responses [150]. This persistent damage is driven not only by the invading pathogens but also by the release of damage-associated molecular patterns (DAMPs), which subsequently trigger persistent immune activation and dysfunction [151]. At present, no effective clinical treatments for sepsis are currently available; therefore, the identification of effective drugs to treat sepsis and improve the long-term outcome represents an urgent need.

In the early stage of sepsis, monocytes, macrophages, and neutrophils in the immune system are continuously activated under the stimulation of pathogens, releasing a large number of proinflammatory cytokines [152]. Itaconate exerts significant anti-inflammatory effects in various mechanisms. In the early stage of severe sepsis, innate immune tolerance represents a profound method to prevent aggravated inflammation [153], which is accompanied by obvious elevation of IRG1 expression and itaconate production [6,154]. Takashi et al. showed that the TCA cycle was significantly reprogrammed to produce a large amount of itaconate in LPS-stimulated mice, which may represent one of the important mechanisms to resist LPS stimulation [155]. Administration of 4-OI prolonged the survival rate of LPS-stimulated mice and suppressed the inflammatory response [6]. These effects may be caused by itaconate on Nrf2-dependent macrophage ferroptosis [156] or caused by direct alkylation of GAPDH, glycolysis inhibition, and the anti-inflammatory effect of itaconate [105]. In addition, the endogenous anti-inflammatory factor HO-1 induced the expression of *IRG1* promoted the production of itaconate, and inhibited the inflammatory response in vivo [157].

Immune suppression in septic patients is related to the later stage of sepsis and is characterized by the reprogramming of cells via epigenetic changes and decreased expression of activating cell surface molecules [152,158]. During immune suppression, infection susceptibility is significantly increased [159]. Macrophages are considered to be tolerant when they are challenged with LPS and rechallenged with LPS 18 h later. This type of macrophage produces enough endogenous itaconate to trigger immune responses and may facilitate a reduction in inflammation [21]. However, during the immune suppression phase, an inadequate response to secondary infections may occur, which can lead to serious conditions. Li et al. found that IRG1 was acetylated and highly expressed in peripheral blood monocytes of patients with sepsis and LPS-tolerized mouse macrophages, triggering the synthesis of large amounts of itaconate [160]. In addition, this synthesized itaconate promoted A20 expression by increasing the modification of histones at the A20 promoter, inhibiting the production of cytokines and increasing the production of ROS and inflammatory factors in LPS-tolerized macrophages [160]. Domínguez-Andrés et al. showed that β-glucan inhibited LPS-induced IRG1 expression, thereby blocking the potentially harmful effects of itaconate on immune suppression [161]. This study, along with previous studies, demonstrated that itaconate metabolism is a crucial regulatory node between immune tolerance and trained immunity.

Mechanistically, sepsis is a complex systemic disease and it is difficult to define the specific targets of itaconate and its derivatives that mediate their anti-inflammatory response to sepsis. We hypothesize that itaconate may act on a combination of numerous targets such as Nrf2, SDH, GAPDH, ALDOA, NLRP3, JAK1, and TET2. More studies are needed to explore the specific mechanism of itaconate in the treatment of sepsis.

6.4. Impact on ischaemia-reperfusion injury (IRI)

Ischaemic injury causes damage to multiple organs and tissues and is one of the leading causes of fatal diseases. In ischemic injury, early recovery of blood flow leads to the recovery of the ischaemic organs, but irreversible damage also occurs. This pathological process is called ischaemia-reperfusion injury (IRI) [162]. During IRI, oxidative stress, inflammation, apoptosis, and fibrosis are all evident. Scientists demonstrated that *IRG1*$^{-/-}$ mice showed exacerbated liver injury after liver IRI, as represented by higher levels of serum alanine transaminase (ALT) and an unfavorable histological analysis. 4-OI treatment reduced apoptotic cell death in the liver after IRI in vitro and in vivo [163]. Zhang et al. demonstrated that preoperative exercise therapy improved the outcomes of patients undergoing surgery. The underlying mechanism of this preventive treatment involves exercise-induced high mobility group box 1 (HMGB1) release, which increases the release of itaconate to impact Kupffer cells in an Nrf2-dependent manner [164].

In addition to liver IRI, itaconate modulates heart IRI, brain IRI, and renal IRI. In heart IRI, itaconate governs TCA cycle remodeling and macrophage activation by inhibiting SDH and regulating inflammatory cytokine production, electron transport chain flow, and ROS production [20]. Moreover, because of the advent of interdisciplinary studies, scientists have developed poly-ε-caprolactone (PCL)/DMI nanofibres [54] and poly (N-isopropylacrylamide-*co*-itaconic acid) microgels [55] to elicit immune responses and cell apoptosis in heart IRI. Brain IRI results in redox imbalance, tissue damage, and neuronal death. After reperfusion, the cells that survive the ischaemic insult suffer from oxidative stress and inflammatory responses [165,166]. Itaconate increases glutathione levels in the brain, reduce ROS and reactive nitrogen species (RNS) levels and improves haemodynamics while reducing leukocyte adhesion to improve neurological function [167]. Itaconate also inhibits M1 microglial polarization and decreases IL-1β expression [168]. In addition, endogenous itaconate plays a role similar to that of 4-OI, and severe brain IRI has been identified in *IRG1*$^{-/-}$ mice [169,170]. IRI is a common cause of renal injury and leads to delayed graft function [171,172]. During renal IRI, tubular epithelial cells are particularly vulnerable, and acute renal injury occurs after renal IRI [173,174]. Zhu et al. demonstrated that during renal IRI, the expression of IRG1 was negatively related to the expression of inflammatory cytokines. IRG1 deficiency aggravated renal IRI in vivo. They found that DI promoted the survival rate of mice with renal IRI and systemic inflammation by enhancing the Nrf2 nuclear translocation [175].

6.5. Impact on oxidative stress

The superfluous flow of free radicals, such as ROS and RNS, causing damage to the activities of cells is known as oxidative stress [176]. Oxidative stress causes the production of DAMPs and cytokine release,

resulting in the release of cytokines and chemokines. Recent studies have reported that Nrf2 plays a significant role in the regulation of oxidative stress [177] and itaconate mainly regulates the Nrf2 pathway to mediate oxidative stress [178]. Heme oxygenase 1 (HO-1) and GSH, which are downstream of Nrf2, play protective role in oxidative stress. In addition, Nrf2 binds to the promoter area of cytokines related to oxidative stress and inhibits the recruitment of RNA polymerase II to repress transcription [63]. As described in '5.2.1 Regulating KEAP1 activity', itaconate increases the alkylation of cysteine residues 151, 257, 273, 288, and 297 on KEAP1, enhances the degradation of KEAP1 and leads to the dissociation and activation of Nrf2. Bambouskova et al. demonstrated that itaconate and DI reacted with glutathione and activated Nrf2 [21], then in the process of periodontal destruction [179], liver fibrosis [72], vitiligo [180], pulmonary fibrosis [181], renal injury [175], osteoporosis [182], and neurodegenerative diseases [183], itaconate and its derivatives functioned as activators of the Nrf2 pathway and attenuated oxidative stress. Moreover, Yi et al. reported that itaconate activated Nrf2 to mitigate oxidative stress in liver IRI, which demonstrated the antioxidant effect in nonimmune cells [163].

7. Perspectives

The recent development of immunometabolism has increasingly piqued the interest of researchers who focus their attention on the interaction between endogenous metabolites, immunity, and inflammatory responses [2,184]. Itaconate, a TCA cycle-derived metabolite, is a promising target for the treatment of certain inflammatory diseases due to its potential anti-inflammatory effects and low toxicity. In this review, we concluded that itaconate regulates inflammatory responses though several methods, providing strong support for the use of metabolites in inflammatory treatments. DMF, a derivative of fumarate, has been approved by the FDA for the treatment of psoriasis and MS. DMF is thought to inhibit glycolysis and immune cell activation in vivo by inhibiting GAPDH, activating the KEAP1/Nrf2 signaling pathway, and modifying GSDMD [4,49,134,185]. Therefore, itaconate may inhibit inflammatory and immune responses in a manner similar to that noted for fumarate. In addition, many questions are worthy of further exploration. For example, how is itaconate generated in vivo? Is there a receptor for itaconate? Do itaconate derivatives play the same role as endogenous itaconate in vivo? How does the modification of specific cysteine residues by itaconate affect the function of proteins? Since previous studies on itaconate were performed in cell and animal models, clinical studies on the roles and specific mechanisms of itaconate in regulating the inflammatory response are required to confirm previous findings and conclusions and to drive an innovative breakthrough in the prevention and treatment of inflammatory diseases.

Author contributions

Xuan Shi and Huanping Zhou are responsible for writing the whole manuscript. Xuan Shi, Wei Mo and Juan Wei are in charge of drawing the pictures in the manuscript. Xin Lv and Quanfu Li are in charge of checking and revision. All authors have read and approved the article.

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Declaration of competing interest

The authors declare no competing interests.

Data availability

No data was used for the research described in the article.

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