Study on the Role and Related Mechanisms of Itaconic Acid in Diseases

Shiyu YU#, Shulin LU#, Jingying QIN#, Ronggeng TAN, Yuxiang MA*

Guilin Medical University, Guilin 541199, China

Abstract This review summarizes the metabolic origin, pharmacological activities, and regulatory mechanisms of itaconic acid at the transcriptional, post-translational modification, and metabolic levels. Its potential application in various diseases is also discussed, providing a theoretical basis for the development of itaconic acid as an anti-inflammatory immunomodulatory agent.

Key words Itaconic acid; Immunometabolism; Anti-inflammatory effects; Disease treatment

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In 1836, itaconic acid was first discovered by Swiss pharmacist Samuel Baup during his study of the thermal decomposition of citric acid. A few years later, it was confirmed that itaconic acid was a product of the thermal decomposition of cis-aconitic acid. However, its medical value was not recognized at the time, and research on it only stayed in industrial application. Itaconic acid is a highly polar α,β-unsaturated dicarboxylic acid with poor membrane permeability[1]. Through the synthesis of various itaconic acid derivatives with enhanced membrane permeability, such as DI, 4-OI, and 4-EI, its biological functions have gradually been discovered. Most studies show that it has anti-inflammatory, antibacterial and antiviral effects. This review elaborates on the role of itaconic acid in diseases and related mechanistic studies, providing insights into its potential value as a therapeutic agent.

Structure and Function of Itaconic Acid

Itaconic acid is an unsaturated dicarboxylic acid, also known as 2-methylidenebutanedioic acid or 2-methylene succinic acid. Due to its high chemical reactivity, it can participate in various addition, polymerization, and esterification reactions. Because itaconic acid does not readily enter cells, modifying its structure into salts or esters enables it to penetrate cells and exert its effects. Itaconic acid resembles succinic acid and fumaric acid structurally, thereby sharing similar biological functions. Studies on these analogous metabolites have significantly expanded the research scope of itaconic acid.

Itaconic acid is a metabolite of tricarboxylic acid (TCA) cycle produced by macrophages, generated through the decarboxylation of cis-aconitic acid derived from citrate dehydration. Studies have shown that itaconic acid is abundantly produced in macrophages activated by lipopolysaccharide (LPS) and interferon-γ (IFN-γ)[2]. It was found that the enzyme encoded by IRG1, cis-aconitate decarboxylase, is responsible for the decarboxylation of cis-aconitate to itaconate in activated macrophages[3], thereby elucidating the biosynthetic pathway of itaconic acid in macrophages. Upon LPS stimulation, macrophages are induced to produce itaconic acid, and an itaconate degradation pathway also exists within macrophages. To date, macrophages and myeloid cells are the only cell types known to be inducibly produce itaconic acid upon stimulation.

Itaconic acid is an important regulator of cellular immunometabolism, playing a key regulatory role in inflammatory responses and oxidative stress. When the tricarboxylic acid cycle is disrupted, itaconic acid accumulates in cells and modulates immune activity through transcriptional regulation, post-translational modification of proteins, and regulation of metabolic enzymes, exerting biological activities such as antibacterial and anti-inflammatory effects[4-5]. Most studies suggest that itaconic acid inhibits inflammation and immune responses in a manner similar to dimethyl fumarate (DMF), a derivative of fumaric acid that has been approved by the FDA for the treatment of psoriasis and multiple sclerosis[6], indicating that itaconic acid holds great potential in immune regulation.

Pharmacological Activities of Itaconic Acid

Anti-inflammatory, antibacterial and antiviral activities

Itaconic acid primarily exerts anti-inflammatory effects within macrophages. As a metabolite derived from the tricarboxylic acid cycle, itaconic acid inhibits succinate dehydrogenase activity in mitochondria, thereby reducing the production of mitochondrial reactive oxygen species and ultimately attenuating the inflammatory response[7]. Furthermore, itaconic acid can shuttle from the

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Shiyu YU (2002-), female, P. R. China, devoted to research about inflammatory immunity.

Shulin LU (2003-), female, P. R. China, major: pharmaceutical preparation.

Jingying QIN (2003-), male, P. R. China, major: science of Chinese materia medica.

#These authors contributed equally to this work.

* Corresponding author.

mitochondrial matrix into the cytoplasm[8]. Most itaconic acid derivatives, such as methylenesuccinic acid, weakly inhibit the production of IL-6 (interleukin-6) and IL-1β in LPS-treated mouse macrophage RAW264.7 cells[9]. Moreover, the chemically synthesized dimethyl itaconate exhibits enhanced cell membrane permeability and has been shown to conjugate with glutathione (GSH) intracellularly[5,10]. Similarly, dimethylalkyl itaconate is predicted to demonstrate stronger anti-inflammatory activity than alkyl itaconate. In the cytoplasm, itaconic acid exerts its anti-inflammatory function primarily through the alkylation of cysteine residues in target proteins via thia-Michael addition reactions. For example, by alkylating the KEAP1 protein and activating the Nrf2 signaling pathway, itaconic acid alleviates inflammatory responses and oxidative stress in macrophages[8,11].

Itaconic acid and its derivatives also exhibit antibacterial activity. Itaconic acid primarily exerts its antibacterial effects by inhibiting the activity of isocitrate lyase in bacteria, thereby blocking the glyoxylate shunt pathway required for bacterial growth and pathogenicity[12]. A notable antibacterial mechanism of itaconic acid involves the inhibition of bacterial isocitrate lyase (ICL), which disrupts the glyoxylate shunt essential for optimal growth and virulence[13-15]. The intermediate metabolite itaconyl-CoA can inhibit the activity of bacterial methylmalonyl-CoA mutase, thereby blocking propionyl-CoA-dependent bacterial growth, as observed in *Mycobacterium tuberculosis*[16]. Compared with the antibiotic streptomycin, butyl itaconate and hexyl itaconate exhibit stronger antibacterial activity against *Acinetobacter*[17].

In tumor cells, itaconic acid derivatives inhibit the replication of Zika virus, herpes simplex virus, and vaccinia virus[18].

Immune regulation and oxidative stress

In lipopolysaccharide (LPS)-activated macrophages, endogenous immunomodulators such as succinate, fumarate, and itaconate accumulate and exert a series of immunoregulatory effects *in vivo*[11,19-21]. In almost all types of pro-inflammatory activation of macrophages, dendritic cells, or neutrophils, significant induction of the enzyme IRG1 is observed. Further studies have demonstrated that itaconic acid exerts an autocrine immunomodulatory role in activated macrophages[8]. In IRG1-deficient mice, when primary macrophages lacking itaconic acid production were stimulated with LPS or LPS plus IFNγ, cytokine production was increased, thereby verifying the anti-inflammatory role of itaconic acid as the primary product of IRG1[8].

Cytotoxicity

Asperitaconic acids A-C showed no cytotoxicity against HepG2 human hepatocellular carcinoma cells or HeLa human cervical epithelioid carcinoma cells at high concentrations[22]. 9-Hydroxyhexyl itaconic acid exhibited cytotoxicity against HeLa cells and MRC-5 human fetal lung fibroblasts, whereas 10-hydroxyhexylitaconic acid showed cytotoxicity only against MRC-5 cells[23]. These findings suggest that the position of the hydroxyl group on the alkyl chain of alkyl itaconates is related to their cytotoxic activity.

Mechanisms of Action of Itaconic Acid

Transcriptional regulation

The transcriptional regulatory role of itaconic acid centers on targeting key transcription factors through multiple pathways to modulate the expression network of inflammation-related genes. Among these, ATF3, Nrf2, and NF-κB are the most representative regulatory targets, collectively maintaining immune homeostasis through synergistic or antagonistic interactions[5,24].

ATF3, as a core negative feedback regulator in immune modulation, serves as a key entry point for itaconic acid-mediated transcriptional regulation. ATF3 directly inhibits Toll-like receptor 4 (TLR4)-mediated inflammatory signaling pathways, and its regulation of type I interferon (IFN I) activity is independent of Nrf2[25]. Studies have shown that after ATF3 knockout, the expression of IκBζ (a key activator of the NF-κB pathway) and pro-inflammatory cytokines such as IL-6 is significantly increased in mouse embryonic fibroblasts. Itaconate and its derivatives can directly inhibit IκBζ activity by upregulating ATF3 expression, thereby blocking the transcriptional activation of pro-inflammatory factors[26]. Furthermore, endogenous itaconate can also regulate IκBζ levels through the same mechanism, forming a negative feedback regulatory axis of "itaconate-ATF3-IκBζ" that effectively suppresses the amplification of inflammatory responses[27].

Nrf2 is a central switch in the transcriptional regulation of cellular antioxidant and anti-inflammatory responses, and itaconic acid modulates its activity through indirect activation. Under normal conditions, Nrf2 binds to KEAP1 and is degraded via ubiquitination. Upon inflammatory or oxidative stress stimulation, itaconic acid modifies cysteine residues of KEAP1 through alkylation, disrupting its binding to Nrf2 and thereby allowing Nrf2 to escape degradation and translocate into the nucleus[11]. In the nucleus, Nrf2 binds to the antioxidant response element (ARE), which activates the expression of antioxidant genes such as HO-1 and NQO1, while directly inhibiting the transcription of pro-inflammatory cytokines including IL-6 and TNF-α, thereby establishing a synergistic "antioxidant-anti-inflammatory" effect[24,28]. In a hepatic ischemia-reperfusion injury model, itaconic acid significantly reduced hepatocyte apoptosis by activating the Nrf2 pathway, confirming the physiological relevance of this regulatory mechanism[29].

NF-κB, as a classic inflammatory transcription factor, is indirectly regulated by itaconic acid. Although itaconic acid does not directly bind to NF-κB subunits, it interferes with its activation through multiple upstream signaling pathways. On one hand, it inhibits IκBζ-mediated NF-κB activation by upregulating ATF3[26]. On the other hand, it reduces the epigenetic activation of NF-κB target genes by inhibiting TET2 activity[30]. Studies have shown that the itaconic acid derivative 4-OI significantly decreases the nuclear translocation level of the NF-κB p65 subunit in LPS-stimulated macrophages, thereby suppressing the expression of genes such as IL-1β and IL-8[24]. Furthermore, the regulation of NF-κB by itaconic acid exhibits cell specificity. In tumor-associated

macrophages, itaconic acid can attenuate the immunosuppressive microenvironment by inhibiting NF-κB activity[24].

Another important feature of transcriptional regulation is the bidirectional modulation of the interferon pathway. Studies have found that itaconic acid derivatives (DI, 4-OI) can effectively inhibit the expression of type I interferons in LPS-stimulated macrophages, whereas unmodified itaconate upregulates interferon levels[31]. This difference may be related to the membrane permeability of the derivatives and their varying activation intensities on ATF3 and Nrf2, suggesting that the transcriptional regulation by itaconic acid is structure-dependent and context-specific[5].

Regulation of protein modifications

Post-translational modification of proteins is a core mechanism through which itaconic acid exerts rapid regulatory effects. Among these, cysteine alkylation is the predominant modification, supplemented by indirect regulation of phosphorylation and ubiquitination, and functional regulation is realized by changing the structure, localization or interaction of target proteins[11,24,32].

Cysteine alkylation relies on the α,β-unsaturated carboxylic acid structure of itaconic acid, which covalently binds to cysteine residues of target proteins via thia-Michael addition. This mechanism plays a central role in anti-inflammatory, antibacterial, and immunomodulatory processes. In the KEAP1-Nrf2 pathway, both 4-OI and endogenous itaconate can alkylate key residues such as Cys151 and Cys273 of KEAP1, disrupting its binding to Nrf2 and its ubiquitin ligase activity, leading to sustained activation of Nrf2[11]. In the regulation of inflammasomes, 4-OI alkylates the Cys548 residue of NLRP3, preventing its interaction with NEK7, thereby inhibiting NLRP3 inflammasome assembly and the maturation of IL-1β[33]. Meanwhile, itaconic acid modifies the Cys77 residue of the pyroptosis protein GSDMD, blocking its pore-forming activity and suppressing the spread of inflammation mediated by pyroptosis. Furthermore, alkylation modifications by itaconic acid on the metabolic enzyme GAPDH, JAK1, and the autophagy-related protein TFEB further expand its regulatory network[34-36].

In addition to direct alkylation, itaconic acid also influences protein function by indirectly regulating phosphorylation states. In the regulation of macrophage polarization, itaconic acid modifies cysteine residues of JAK1, thereby inhibiting the phosphorylation and activation of JAK1 and its downstream STAT6, thus blocking M2 macrophage differentiation and alleviating M2 polarization-related diseases such as fibrosis[34]. In innate immunity, alkylation of TFEB by 4-OI disrupts its phosphorylation state, promotes TFEB nuclear translocation, activates the expression of lysosome biogenesis-related genes, and enhances bacterial clearance[35]. Furthermore, itaconic acid inhibits succinate dehydrogenase (SDH), leading to succinate accumulation and indirectly regulating the phosphorylation and stability of HIF-1α, which serves as an important indirect pathway influencing inflammatory transcription[7-8].

Regulation of ubiquitination modifications primarily focuses on the degradation process of Nrf2. As previously described, itaconic acid inhibits the E3 ubiquitin ligase activity of KEAP1 through alkylation, reducing the ubiquitin-mediated degradation of Nrf2, a representative example of itaconic acid-mediated regulation of protein ubiquitination[11]. Currently, no evidence has been found that itaconic acid directly regulates the activity of ubiquitin ligases or deubiquitinating enzymes. It is speculated that its effect on ubiquitination is primarily achieved through alkylation of the substrate recognition subunits of ubiquitin ligases[24].

Metabolic regulation

Itaconic acid is a byproduct of the tricarboxylic acid cycle and participates in metabolic regulation. During inflammatory responses and oxidative stress in macrophages, intracellular oxidative phosphorylation levels decrease while glycolysis increases. Itaconic acid can inhibit glycolysis by targeting GAPDH, thereby exerting anti-inflammatory effects[36]. Furthermore, itaconic acid can compete with succinate for the active site of succinate dehydrogenase (SDH), effectively inhibiting SDH activity and preventing the oxidation of succinate to fumarate. This thereby blocks the generation of mitochondrial reactive oxygen species (mtROS) driven by mitochondrial respiratory chain complex I and effectively suppresses inflammatory responses[7-8].

Applications of Itaconic Acid in Diseases

Autoimmune diseases

Autoimmune diseases are a group of inflammatory disorders that commonly affect the joints, muscles, bones, tendons, and ligaments, and sometimes involve other organs of the body. Major autoimmune diseases include systemic lupus erythematosus (SLE), multiple sclerosis (MS), psoriasis, rheumatoid arthritis (RA), and cryopyrin-associated periodic syndromes (CAPS)[37]. Studies have found that the expression of itaconic acid is significantly reduced in the blood of patients with SLE[38]. Meanwhile, the itaconic acid derivatives 4-OI and DI can effectively alleviate patient symptoms. By analyzing serum, urine, and synovial fibroblasts at different stages of RA progression, it was found that itaconic acid is closely associated with the onset and development of the disease and may serve as a disease biomarker for RA[39-40]. Research has also indicated that itaconic acid plays an important role in the pathogenesis of RA[41].

Inflammatory responses induced by viral infections

Itaconic acid plays an important role in virus-induced inflammatory responses. Studies have found that in COVID-19 patients, citramalyl-CoA lyase (CLYBL) is significantly upregulated, converting itaconic acid into acetyl-CoA and leading to decreased levels of itaconic acid[18]. Meanwhile, 4-OI directly inhibits the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and also limits excessive interferon activation by modulating NRF2 activity, thereby suppressing inflammatory responses and alleviating clinical symptoms in patients[18].

However, itaconic acid can sometimes exert opposing effects and accelerate viral replication. During vesicular stomatitis virus (VSV) infection, IRG1 is overexpressed, and itaconic acid

promotes the production of ROS and inflammatory cytokines, leading to lung tissue damage. In contrast, IRG1$^{-/-}$ mice effectively suppress VSV infection[42].

Sepsis

Sepsis is a complex systemic disease in which innate immune tolerance plays an important role during the early stage of severe sepsis[43], accompanied by a significant increase in IRG1 expression and itaconic acid production[44]. Studies have shown that when mice are stimulated with LPS, the TCA cycle is altered, leading to substantial itaconic acid production, suggesting that itaconic acid is one of the key mechanisms in resisting LPS stimulation[44]. Both 4-OI and endogenous HO-1 can inhibit inflammatory responses[44]. Most studies suggest that itaconate metabolism serves as a key node between immune tolerance and memory innate immune response[24]. However, the specific mechanisms by which itaconate treats sepsis require further investigation.

Ischemia-reperfusion injury

Ischemia-reperfusion injury (IRI) refers to the phenomenon in which early restoration of blood flow following ischemic injury leads to the recovery of the ischemic organ, but may also result in irreversible damage[45]. During IRI, oxidative stress, inflammation, apoptosis, and fibrosis are prominent. Studies have found that both *in vitro* and *in vivo*, 4-OI reduces apoptotic cell death in the liver following IRI[29]. In cardiac IRI, itaconic acid regulates TCA cycle reprogramming, macrophage activation, and the production of inflammatory cytokines and ROS by inhibiting SDH, thereby reducing myocardial injury[46]. Itaconic acid also increases glutathione levels in the brain and improves neurological function[47]. Itaconic acid has shown therapeutic efficacy in both cerebral IRI and renal IRI[47-48]. Studies have found that itaconic acid can also alleviate inflammatory responses by inhibiting M1 microglial polarization and reducing IL-1β expression[47].

Oxidative stress injury

During oxidative stress, Nrf2 can bind to the promoter regions of oxidative stress-related cytokines, inhibiting the recruitment of RNA polymerase II and suppressing transcription, thereby mitigating the onset of oxidative stress[28]. Itaconic acid and its derivatives, as activators of the Nrf2 pathway, activate Nrf2 and consequently alleviate oxidative stress[11].

Summary and Prospects

Itaconic acid, as a derivative of the tricarboxylic acid cycle, has been shown in numerous studies to possess potential anti-inflammatory effects, making it a promising new target and direction for the treatment of certain diseases[24]. DMF, a derivative of fumaric acid, has been approved by the FDA for the treatment of psoriasis. It is believed to inhibit glycolysis and immune cell activation *in vivo* by suppressing GAPDH, activating the Keap1/Nrf2 signaling pathway, and modifying GSDMD[49]. Therefore, itaconic acid may inhibit inflammatory and immune responses in a manner similar to fumaric acid. However, current research on itaconic acid remains limited. Key questions, such as how itaconic acid is generated *in vivo*, whether it has specific receptors, and whether the effects of itaconic acid derivatives are consistent with those of endogenous itaconic acid, still warrant further in-depth investigation[24]. Previous studies have been conducted based on cellular and animal models. If its mechanisms of action could be investigated in clinical settings, it might drive innovative breakthroughs in the prevention and treatment of inflammatory diseases with itaconic acid.

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