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Review

The cell autonomous and non-autonomous roles of itaconate in immune response

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ABSTRACT

Itaconate which is discovered as a mammalian metabolite possessing antimicrobial and immunoregulatory activity has attracted much attention in the field of immunometabolism. Itaconate is synthesized by myeloid cells under conditions of pathogen infection and sterile inflammation. In addition to regulating immune response of myeloid cells, itaconate secreted from myeloid cells can also be taken up by non-myeloid cells to exert immunoregulatory effects in a cell non-autonomous manner. In this review, we recap the discovery of itaconate as a distinct immunologic regulator and effector, describe the development of itaconate biosensor, and detail the recent findings that decipher the mechanism underlying intercellular transport of itaconate. Based on these knowledges, we propose itaconate is a messenger transmitting immunologic signals from myeloid cells to other types of cells during host inflammation and immune defense.

1. Introduction

Activation of immune cells in responding to pathogen invasion and tissue injury is accompanied by metabolic rewiring. During metabolic rewiring induced by immune activation, dramatic changes in cell-intrinsic metabolite levels occur and specific metabolites have been shown to regulate immune response independent of their roles in energy production. In particularly, one example of metabolite with immunoregulatory property is itaconate, which was described as a metabolite possessing dual effects of anti-inflammation and anti-bacteria. A series of studies reported that itaconate production is almost exclusively confined in activated myeloid cells, such as tumor-associated macrophages (Chen et al., 2023; Wang et al., 2023; Weiss et al., 2018), tumor-infiltrating neutrophils (Zhao et al., 2023), tumor-infiltrating polymorphonuclear myeloid-derived suppressor cells (Zhao et al., 2022), and dendritic cells (Jaiswal et al., 2022). In this review, we explore the implications of recent findings regarding itaconate as an immunologic regulators and effectors, describe the development of itaconate biosensor, detail the mechanism of itaconate intercellular transport, and discuss role of itaconate as an immunotransmitter.

2. Itaconate metabolism in mammalian cells

While itaconate was first identified as a building block of industrial polymers and bioactive compounds (Okabe et al., 2009), a series of studies demonstrate that itaconate may function as an important regulator and effector in mammalian immune response. In 1995, Lee et al. identified the gene of immune-responsive gene 1 (*IRG1*) which was highly upregulated in lipopolysaccharide (LPS)-treated macrophages, although there is no well-defined function for *IRG1* at that time (Lee et al., 1995). Then in 2011, several groups reported the presence of mammalian itaconate production in the contexts of different immune settings: in the pulmonary tissue of *Mycobacterium tuberculosis* (MTB)-infected mice (Shin et al., 2011), in the cell extracts and culture supernatants of LPS-stimulated RAW264.7 and VM-M3 murine macrophage cell lines (Strelko et al., 2011; Sugimoto et al., 2012). In 2013, Michelucci et al. demonstrated that the *IRG1*-encoded mitochondrial enzyme, named aconitate decarboxylase 1 (ACOD1), produces itaconate by catalyzing decarboxylation of the tricarboxylic acid (TCA) cycle intermediate *cis*-aconitate in mammalian cells (Michelucci et al., 2013)

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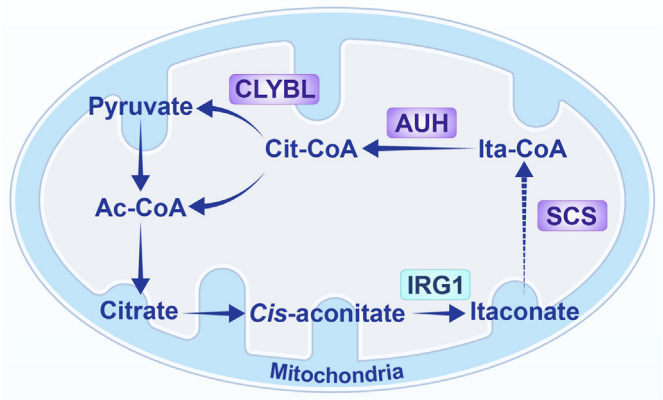

Fig. 1. The metabolism of itaconate in mammalian cells. In mitochondria, itaconate is synthesized from *cis*-aconitate by IRG1 and then metabolized to pyruvate and acetyl-CoA via three sequential steps catalyzed by SCS, AUH, and CLYBL. Ita-CoA, itaconyl-CoA; Cit-CoA, citramalyl-CoA; Ac-CoA, acetyl-CoA; IRG1, immune-responsive gene 1; SCS, succinyl coenzyme A synthetase; AUH, methylglutaconyl-CoA hydratase; CLYBL, citramalyl-CoA lyase.

(Fig. 1). Due to this finding, which establishes the connection between *IRG1* and itaconate, *IRG1* and its encoded protein were also referred to as *ACOD1* (*Acod1* for mouse) and ACOD1, respectively. Several naturally occurring *IRG1* variants that structurally affect itaconate synthesis activity of IRG1 have been observed in humans (Chen et al., 2019). Elucidation of the crystal structure of IRG1 may address many questions essential to the chemistry, biology, evolution, and medical importance of itaconate synthesis.

In contrast to anabolism, itaconate catabolism most likely occurs in mammalian liver mitochondria through multiple reactions. Firstly, itaconate is converted to itaconyl-CoA by succinyl coenzyme A synthetase (SCS), itaconyl-CoA is hydrated to citramalyl-CoA by methylglutaconyl-CoA hydratase (AUH), then citramalyl-CoA is lysed to pyruvate and acetyl-CoA by citramalyl-CoA lyase (CLYBL, also known as citrate lyase subunit beta-like) (Adler et al., 1957; Shen et al., 2017; Wang et al., 1961) (Fig. 1). It was also reported that succinyl-CoA:glutarate-CoA transferase (SUGCT) can convert itaconate into itaconyl-CoA in the developing erythrons (Marcero et al., 2021). Moreover, itaconyl-CoA, an intermediate of itaconate catabolism, has been reported to irreversibly inactivate vitamin B_{12} (Ruetz et al., 2019), thereby depleting vitamin B_{12} in inflammatory or CLYBL-deficient macrophages (Shen et al., 2017). In addition, two endogenous isomers of itaconate, mesaconate and citraconate, which display differences in terms of their electrophilic and immunoregulatory properties, have been found in inflammatory macrophages (Chen, Elgaher, et al., 2022; He et al., 2022). Given that their similar function in terms of immunoregulation to itaconate, further studies investigating the metabolism of these two itaconate isomers in immune cells are warranted.

3. Immunoregulatory and antibacterial role of itaconate

As an endogenous metabolite containing an electrophilic α, β-unsaturated carboxylic acid group, itaconate can covalently modify the cysteine residues of proteins through a Michael addition-based mechanism, which is also termed alkylation (Mills et al., 2018; Qin et al., 2019). Our previous study reported that transcription factor EB (TFEB) is alkylated and activated by itaconate, itaconate-mediated TFEB activation induces lysosomal biogenesis, thereby promoting macrophagic antibacterial innate immunity (Zhang et al., 2022). Itaconate can also alkylate cysteine residues in aldolase A (ALDOA) (Qin et al., 2019) and gasdermin D (GSDMD) to regulate immune response (Bambouskova et al., 2021). Recently, another study demonstrated that thimerosal, a vaccine preservative, can induce tumor-intrinsic IRG1 expression and itaconate production to enhance tumor immunogenicity through upregulating TFEB-mediated antigen presentation (Wang et al., 2024). As a cell-intrinsic metabolite, itaconate acts as an inhibitor for ten-eleven translocation (TET) DNA dioxygenases (Chen, Morcelle, et al., 2022) and succinate dehydrogenase (SDH) (Cordes et al., 2016; Lampropoulou et al., 2016) to restrain the inflammatory response; however, it was also reported that itaconate boosts LPS-stimulated interferon-β production in macrophages (O'Carroll et al., 2024; Swain et al., 2020). Moreover, itaconate can induce activating transcription factor 3 (ATF3)-dependent stress responses (Bambouskova et al., 2018), alleviate pulmonary fibrosis (Ogger et al., 2020), and strengthen host defense against infection of Zika virus (Daniels et al., 2019), influenza A virus (Sohail et al., 2022) and *Coxiella burnetii* (Kohl et al., 2023). In addition, *Irg1*-knockout mice display enhanced sensitivity to cancer immunotherapy (Chen et al., 2023; Gu et al., 2023; Wang et al., 2023; Zhao et al., 2022, 2023), severe atherogenesis (Cyr et al., 2024; Song et al., 2023), and improved immune control of *Plasmodium* (Ramalho et al., 2024) compared with wild-type mice, suggesting an immunoregulatory role for itaconate *in vivo*.

Besides its immunoregulatory function, itaconate was found to be an antibacterial compound that can kill bacteria by inhibiting isocitrate lyase (ICL), an essential enzyme in bacteria that use the glyoxylate shunt as energy source (Kwai et al., 2021; Rittenhouse & McFadden, 1974), and restrict the replication of intravacuolar bacterial pathogens depending on a Rab guanosine triphosphatase (GTPase) pathway in macrophages (Chen et al., 2020). Likewise, another study reported that TFEB-driven itaconate synthesis restrains *Salmonella* Typhimurium burden in macrophages via exposing the intravacuolar bacteria to elevated itaconate levels (Schuster et al., 2022). Moreover, itaconate-derived itaconyl-CoA was found to inhibit MTB growth on propionate via inactivating the glyoxylate shunt-related enzyme B_{12}-dependent methylmalonyl-CoA mutase (MCM) (Ruetz et al., 2019). Collectively, these findings suggest that itaconate may be a metabolite possessing dual functions of immunoregulation and bactericide.

In addition to the abovementioned cell-intrinsic functions, itaconate also exerts cell-extrinsic functions in several immune-related contexts. Exogenous itaconate impaired the antitumor effector function of $CD8^+$ T cells (Zhao et al., 2022), promoted pulmonary mucociliary clearance via activating the G protein-coupled receptor 2-oxoglutarate receptor 1 (OXGR1) in a mouse model of bacterial infection (Zeng et al., 2023), and ameliorated autoimmunity by modulating the balance of T cell differentiation (Aso et al., 2023). These data raise the possibility that itaconate synthesized and secreted by myeloid cells may act as an immunotransmitter.

4. Immunoregulatory role of itaconate derivatives

Akin to the unmodified itaconate, some itaconate derivatives, such as 4-octyl itaconate (OI) and dimethyl itaconate (DI), which are cell-permeable and possess stronger electrophilicity than itaconate (Swain et al., 2020), may also exert immunoregulatory function. In particularly, OI was reported to limit inflammatory response by alkylating cysteine residues on multiple proteins, including kelch-like ECH-associated protein 1 (KEAP1) (Mills et al., 2018); glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (Liao et al., 2019); Janus kinase 1 (JAK1) (Runtsch et al., 2022); nucleotide-binding oligomerization domain (NOD)-, leucine-rich repeat (LRR)-, and pyrin-domain-containing protein 3 (NLRP3) (Hooftman et al., 2020); stimulator of interferon genes (STING) (Su et al., 2023); and mitochondrial antiviral signaling (MAVS) and inhibitory kappa B kinase beta (IKKβ) (Kurmasheva et al., 2024). However, due to the differences in structural and electrophilic properties of OI and unmodified itaconate, further studies are needed to examine whether the similar effects can be observed from treatments with OI and unmodified itaconate.

5. Development of an itaconate biosensor

To detect the influx and efflux of itaconate in living cells, a genetically encoded fluorescent itaconate biosensor, referred to as BioITA (biosensor for itaconate), was developed by coupling a circularly permuted green fluorescent protein (cpGFP) into an itaconate-binding domain (IBD) derived from a bacterial LysR-type transcriptional regulator (Sun et al., 2022). Utilizing BioITA, mitochondrial and cytosolic concentrations of itaconate in LPS-stimulated RAW264.7 macrophages were determined as 551 μM and 1757 μM, respectively (Sun et al., 2022). This study indicates that BioITA is capable of detecting itaconate dynamics with subcellular resolution in living cells, which provides a powerful tool for further investigating the unknown biological functions of itaconate.

6. Immunotransmitter role of itaconate

Previous studies reported that IRG1 expression can be detected in myeloid cells, but not non-myeloid cells, in inflammatory microenvironment, suggesting that itaconate may be specifically synthesized in inflammatory myeloid cells. Given that itaconate also regulate inflammatory responses in a cell-extrinsic manner, it is possible that itaconate released from IRG1-expressing myeloid cells can be delivered to non-myeloid cells that do not express IRG1.

Utilizing BioITA as a tool for readout, our group performed a clustered regularly interspaced short palindromic repeat (CRIPSR)/Cas9-based genetic screen and found that intracellular itaconate is exported by ATP-binding cassette transporter G2 (ABCG2) in inflammatory macrophages (Chen, Zhang, et al., 2024). Deficiency of ABCG2-mediated itaconate export resulted in increase of transcription factor TFEB-dependent lysosomal biogenesis and antibacterial innate immunity (Chen, Zhang, et al., 2024). This study identifies ABCG2 as an itaconate exporter and characterize the role of ABCG2-mediated itaconate export in antibacterial innate immunity, suggesting that pharmacological intervention of ABCG2-mediated itaconate export has potential for treating human bacterial infections.

Next, our group performed a CRIPSR/Cas9-based genetic screen akin to the screen of itaconate exporter and found that solute carrier family 13 member 3 (SLC13A3) is a dominant itaconate importer in hepatocytes (Chen, Liu, et al., 2024). Functional studies revealed that liver-specific *Slc13a3*-knockout mice manifested impaired hepatic antibacterial innate immunity. Mechanistically, SLC13A3-mediated itaconate uptake induces TFEB-dependent lysosomal biogenesis and subsequently improves antibacterial innate immunity in mouse hepatocytes (Chen, Liu, et al., 2024). This finding thus identifies SLC13A3 as a dominant itaconate importer in hepatocytes and will aid in the development of more effective itaconate-based antibacterial therapeutics. Taken together, as shown in Fig. 2, these findings decipher the mechanism of itaconate intercellular transport and provide evidences to strongly support itaconate functions as an immunotransmitter in host antibacterial immune defense. In addition, Lin et al. recently reported that SLC13A3-mediated uptake of macrophage-derived itaconate impairs tumor immunity via endowing tumor ferroptosis resistance (Lin et al., 2024), suggesting that the SLC13A3 may be a promising immunometabolic target for treating SLC13A3-positive cancer.

7. Concluding remarks

Closely integrated and mutual regulation between metabolic changes and immune cell activation is crucial for mounting appropriate host immune response. Rapid metabolic rewiring occurs in response to

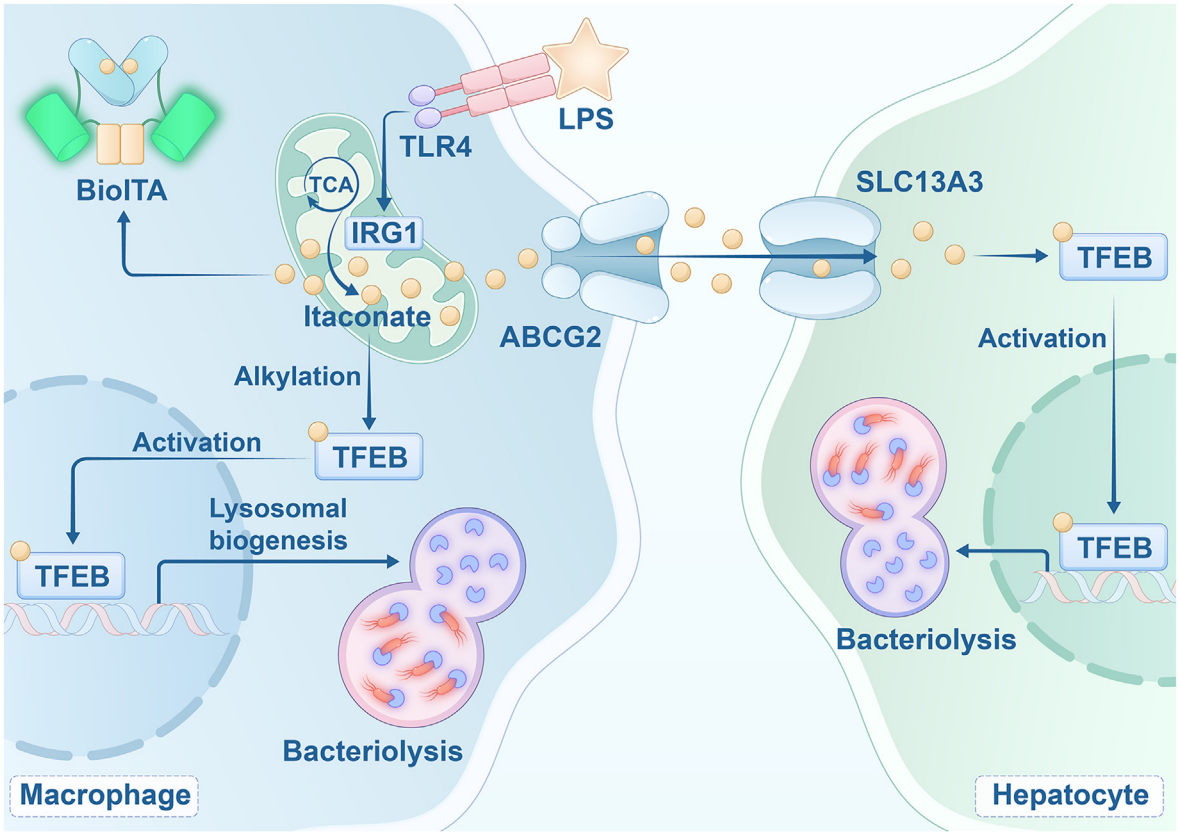

Fig. 2. The mechanism of itaconate intercellular transport. ABCG2 and SLC13A3 are identified as the exporter and importer of itaconate, respectively. ABCG2-mediated itaconate export is a key regulatory mechanism that limits TFEB-dependent lysosomal biogenesis and antibacterial innate immunity in inflammatory macrophages. SLC13A3-mediated itaconate uptake improves hepatic antibacterial innate immunity. BioITA serves as a genetically encoded fluorescent biosensor for detecting intracellular itaconate in living cells. TLR4, Toll-like receptor 4.

inflammatory stimuli and may dictate immune cell fates by meeting cellular metabolic demands. In addition to their originally defined roles in bioenergy and biosynthesis, metabolites can also perform as signaling molecules, such as acting as messengers to deliver cellular signals. Remarkably, the finding that itaconate is an immunoregulatory metabolite capable of being transported between different cell types will shed light on the mechanisms underlying itaconate regulates inflammatory responses and will make the potential utility of itaconate as an anti-inflammatory and antibacterial drug. As discussed in the Review, accumulating evidences support that itaconate may be a metabolite possessing messenger property. Given the nature of the rapid, precise, dynamic and integrated regulation conveyed by metabolites, we expect more metabolites with similarity to itaconate that function as immunotransmitters in host immune response to be discovered.

CRediT authorship contribution statement

Chao Chen: Writing – review & editing. **Xinjian Li:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

Xinjian Li reports financial support was provided by the Institute of Biophysics Chinese Academy of Sciences and the National Natural Science Foundation of China. Xinjian Li reports a relationship with Institute of Biophysics Chinese Academy of Sciences that includes: employment. If there are other authors, they 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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