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Review Article

Emerging role of the itaconate-mediated rescue of cellular metabolic stress

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Abstract

Metabolic regulations play vital roles on maintaining the homeostasis of our body. Evidence have suggested that ATF3 and nuclear factor erythroid 2–related factor 2 (NRF2) are critical for maintaining cell function, metabolism, and inflammation/anti-inflammation regulations when cells are under stress, while the upstream regulators in the stressed cells remain elusive. Recent findings have shown that tricarboxylic acid cycle metabolites such as itaconate and succinate are not just mitochondrial metabolites, but rather important signaling mediators, involving in the regulations of metabolism, immune modulation. Itaconate exerts anti-inflammatory role through regulating ATF3 and NRF2 pathways under stressed conditions. In addition, itaconate inhibits succinate dehydrogenase, succinate oxidation and thus blocking succinate-mediated inflammatory processes. These findings suggest itaconate-ATF3 and itaconate-NRF2 axes are well-coordinated machineries that facilitate the rescue against cellular stress. Here, we review these fascinating discoveries, a research field may help the development of more effective therapeutic approach to manage stress-induced inflammation, tissue damage, and metabolic disorder.

Keywords: *ATF3, Inflammasome, Itaconate, Mitochondrial stress, Nuclear factor erythroid 2–related factor 2*

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Itaconate is a metabolite conducting cellular signaling and modulating immune response

To release energy through the oxidation of organic compounds, the tricarboxylic acid (TCA) cycle (also known as citric acid cycle or Krebs cycle), is a series of chemical reactions involving metabolites with cellular signaling properties [1]. Those microRNAs regulating the metabolic pathways are thus influence the inflammation outcomes [2]. TCA cycle metabolites, including itaconate, succinate, α-ketoglutarate, 2-hydroxyglutarate, fumarate, were shown to exert various cellular signaling properties [1,3-9]. Among these, itaconate, a metabolite with anti-inflammatory property, is derived from the decarboxylation of TCA cycle intermediate cis-aconitate [1]. The immune-responsive gene 1 protein (IRG1) is the enzyme responsible for itaconate production. Lipopolysaccharide (LPS) induces IRG1 to result the accumulation of itaconate, which subsequently reduces interleukin (IL)-1β production [1]. IRG1 deficiency in mice led to the elevation of pro-inflammatory cytokines interleukin (IL)-1β, IL-18, IL-6, IL-12 production during macrophage activation by LPS treatments [10]. IRG1 deficiency also led to increased mortality and lung inflammation in a mouse model of *Mycobacterium tuberculosis* infection [11]. These results suggest that itaconate is critical infection-induced feedback regulating factor that limits excessive inflammation. Itaconate derivatives, such as 4-Octyl itaconate (4-OI), inhibit aerobic glycolysis by targeting glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase, interferon and inflammasome to exert anti-inflammatory effects [12,13]. Overall, these studies highlight that itaconate is not just a mitochondria metabolite but rather an important signaling molecule involved in the regulations of metabolism, immune modulation, and gene expression [Figure 1] [1,3-9].

Anti-inflammatory effects of itaconate derivatives

Anti-inflammatory effects of itaconate have been associated with inhibition succinate dehydrogenase (SDH) [Figure 1] [10,14], and down-regulation of inflammasome and pro-inflammatory cytokines [5,10]. The 4-OI is a most studied itaconate derivative, displaying anti-inflammatory effects [12,13,15]. For example, 4-OI reduced the activity of pro-inflammatory cytokine IL-1β in LPS-treated mouse and human macrophages and rescued

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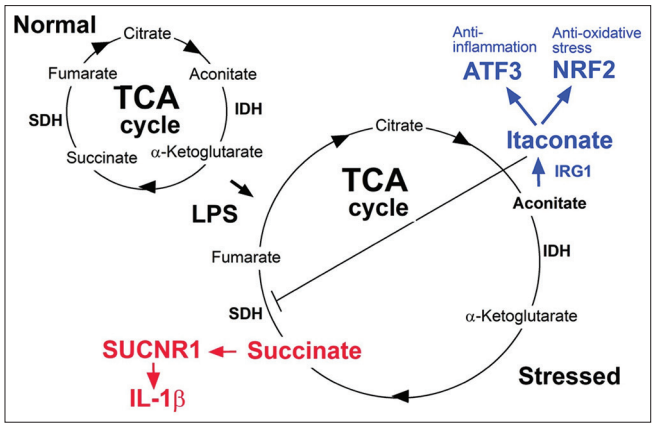

Figure 1: Itaconate-induced cell protective anti-stress responses. Inflammatory stimulus such as LPS upregulates the expression of CAD (also known as IRG1), an enzyme converts cis-aconitate to itaconate in the mitochondria [4]. LPS-induced cellular activation leads to glycolytic flux and the transition towards an anaplerotic TCA cycle with high production levels of itaconate [9]. High itaconate levels suppress SDH, blocking succinate-mediated inflammatory processes and inducing the anti-inflammatory proteins NRF2 and cyclic ATF3 [9]. Succinate may enhance proinflammatory cytokine IL-1β pathway through SUCNR1 [3]. Those blue labels indicate the anti-inflammatory and anti-oxidative-stress responses; those red labels indicate proinflammatory responses. LPS: Lipopolysaccharide, CAD: Cis-aconitate decarboxylase, IRG1: Immune-responsive gene 1, SDH: Succinate dehydrogenase, NRF2: Nuclear factor erythroid 2-related factor 2, ARF3: AMP-dependent transcription factor 3, SUCNR1: Succinate receptor 1, IDH: Isocitrate dehydrogenase

LPS injection-induced mortality in mice [15]. Treatments of 4-OI ameliorated LPS-stimulated pro-inflammatory cytokines IL-1β, IL-6, and tumor necrosis factor (TNF)-α production in human peripheral blood mononuclear cells (PBMCs) and THP-1 macrophages is associated with the activation of the nuclear factor erythroid 2–related factor 2 (NRF2) pathway [16]. Such 4-OI-mediated NRF2–dependent anti-inflammation can also limit the expression of type I interferon (IFN) [17]. These results collectively suggested that itaconate is an anti-inflammatory metabolite. In addition to 4-OI, some other itaconate derivatives were found to have more or less anti-inflammatory and immune-modulating effects. For example, evidence have shown that both dimethyl itaconate and 4-octyl itaconate induce immunosuppressive phenotypes in an NRF2-independent manner, which associated with inhibited IκBζ and pro-interleukin (IL)-1β induction, as well as pro-inflammatory cytokines IL-6, and interferon-β secretion [13].

Itaconate-induced anti-inflammatory ATF3 pathway

Recently, it is shown that itaconate conducts anti-inflammatory effects primarily mediating through at least 3 downstream pathways: Pathway 1, Cyclic AMP-dependent transcription factor (ATF3); pathway 2, NRF2 [9]; pathway 3, itaconate-mediated inhibition on inflammasome-IL-1 axis [5].

ATF3 is an anti-inflammatory, basic region-leucine zipper (bZip) DNA binding domain containing transcription factors [18]. By forming dimers with ATF3-itself and various other bZip proteins, such as ATF2, c-Jun, JunB, and JunD, ATF3 can function as a transcriptional activator or repressor [19,20]. Evidence have suggested that ATF3 plays a role in a variety of biological processes, such as metabolism [20,21], cell motility [22], cell cycle [23], DNA repair [24], cell death [25], and various functions on maintaining the homeostasis [26-37]. ATF3 can be up-regulated by stimulations from wide spectrum of toll-like receptors (TLRs), including TLR4, 2/6, 3, 5, 7, and 9, and serves as a negative feedback regulator [38]. For example, ATF3 limits the release of pro-inflammatory cytokine high mobility group box 1, which results in lung injury after LPS challenge [33]. ATF3 also limits LPS-induced chemokine (C-X-C motif) ligand 1 production in mouse airways [22]. Basal and LPS-stimulated chemokine (C-C motif) ligand 4 (CCL4) mRNA and protein levels are higher in the bone-marrow-derived macrophages (BMDMs) of ATF3 deficient (*ATF3*$^{-/-}$) mice compared with those of wild type (*ATF3*$^{+/+}$) mice [39]. Consistently, primary macrophages from *ATF3*$^{-/-}$ mice exhibit increased production of IL-6 and IL-12p40 cytokines following TLR activation [38]; LPS induces higher IL-6 and IL-12 mRNA levels in BMDMs of *ATF3*$^{-/-}$ mice [40]. Such anti-inflammatory effect of ATF3 is in part mediating through the interact with histone deacetylase 1, leading to histone deacetylation and suppression of IL-6 and IL-12b promoter activity in LPS-treated macrophages [40]. Accordingly, ATF3 was suggested negatively regulating the gene expression of those pr-oinflammatory cytokines containing ATF/CREB binding sites [40]. Additionally, comparisons of wild type and gene knockout mice, evidence have shown that dimethyl itaconate (DI) inhibits LPS-mediated IκBζ induction in mouse BMDMs and ameliorates IL-17-mediated IκBζ induction, and associated psoriatic pathology in mice in an ATF3-dependent but NRF2-independent manner [41]. These results revealed that the itaconate-ATF3 axis exerts an anti-inflammatory role.

In addition to inflammation, mitochondrial stress also induces ATF3 expression [42]. ATF3 was shown to involve in adipocyte hypoxia-mediated mitochondrial regulation [43]. Inhibition of ATF3 expression increased mitochondrial stress and induced cytochrome C release [44]. In addition, ATF3 suppresses PTEN-induced putative kinase 1 gene expression in lung epithelial cells to control mitochondrial homeostasis [45]. In other words, itaconate is a native ATF3 inducer, which couples to metabolic regulation.

Itaconate and nuclear factor erythroid 2–related factor 2 pathway

NRF2 is an anti-oxidative stress and anti-inflammatory, bZip DNA binding domain-containing transcription factor [46]. Itaconate is transported from the mitochondria to the cytoplasm, where it shows its functions via the carriers that transport dicarboxylate and citrate [15]. In the cytosol, itaconate uses its electrophilic α,β-unsaturated carboxylic acid to alkylate the cysteine residues on Kelch-like ECH-associated protein-1 (KEAP1) that normally binds and promotes proteasome degradation of NRF2 [15]. Similar to the modification of cysteines by fumarate itaconate activates NRF2 by alkylation of KEAP1 cysteine residues. Because 4-OI stabilized V5-tagged NRF2 (NRF2–V5) in COS1 cells co-expressing wild-type KEAP1 but not a cysteine 151 (Cys151)-Ser mutant, Cys151 is a sensor on KEAP1 for

itaconate [15]. KEAP1 alkylation allows newly synthesized NRF2 to accumulate and translocate into the nucleus to activate the anti-oxidant and anti-inflammatory gene expression [6]. Accordingly, itaconate is a native NRF2 inducer, which couples to metabolic regulation. By binding to the promoters, NRF2 inhibits the expression of pro-inflammatory genes IL-1β and IL-6 [47]. Similarly, the itaconate derivative 4-OI activates NRF2 signaling to inhibit pro-inflammatory cytokine production in PBMCs [16].

Itaconate and succinate-inflammasome-IL-1 axis

Immune system defenses against external stimulations and pathogen invasions [48-57], in which the inflammasome-IL-1 axis exerts critical role on the induction of inflammation in various conditions [58-70]. Itaconate was demonstrated to inhibit SDH, and subsequently succinate oxidation and thus blocking succinate-mediated inflammatory processes [10,14]. Succinate was shown to induced the pro-inflammatory IL-1 pathway through succinate receptor 1 [71]. By contrast, itaconate and 4-OI specifically inhibited NLRP3 activation, but not AIM2 or NLRC4 inflammasomes [5]. Conversely, NLRP3 activation was increased in itaconate-depleted *Irg1*$^{-/-}$ macrophages [5]. In addition, 4-OI inhibited NLRP3-dependent IL-1β release from PBMCs isolated from cryopyrin-associated periodic syndrome patients, and reduced inflammation in an *in vivo* model of urate-induced peritonitis [5]. These results suggest a negative role of itaconate on inflammation.

Metabolic brake model

For easier explanation, here we postulate a simplified model, in which itaconate-ATF3 and itaconate-NRF2 axis are critical metabolic brakes on maintaining metabolic homeostasis to achieve anti-inflammation and tissue repair [Figure 2]. When cells are under inflammation, metabolic overload, itaconate levels are increased [Figure 1], by which metabolic brakes-induced physiological metabolic brake responses exert ameliorative roles to reduce metabolic stress (e.g., inflammation, metabolic diseases, tissue damages)-elicited adverse effects. Thus, without ATF3, other molecular brake become more rapidly wore down by stresses [Figure 2].

Conclusions

Because NRF2 and its principal negative regulator KEAP1 are critical in the maintenance of redox, metabolic, and inflammation, the activators and inhibitors of NRF2 have been considered as therapeutic agents in chronic diseases [72-74]. Similarly, cardiac ATF3 exerts a protective role on the amelioration of high fat diet-induced cardiac remodeling processes [75]. Overexpression of ATF3 induced the trans-differentiation of white adipocytes into beige/brown adipocytes *in vitro* [76]. Chemical ATF3 inducer sulfuretin counteracts weight gain and improves glucose tolerance in an ATF3 dependent manner, indicating that ATF3 induction can be a molecular target for preventing obesity and metabolic diseases [77]. It is also shown that ST32da, a chemically synthesized ATF3 inducer, enhances ATF3 expression to inhibit

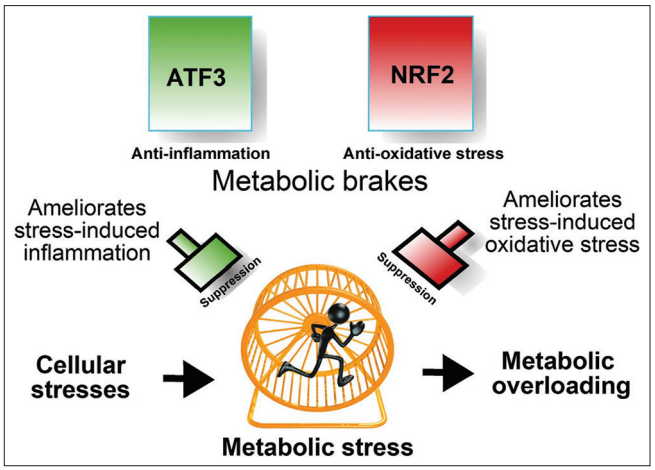

Figure 2: The metabolic brake model. Itaconate-mediated regulations (e.g. itaconate-ATF3, itaconate-NRF2 axes) serve as potential "metabolic brakes" to conduct anti-inflammation, anti-oxidant and tissue repair effects. The "metabolic brake" exerts ameliorative roles on metabolic stresses (e.g. oxidative stress, excessive inflammation, metabolic overload, obesity) induced adverse effects. The image of wheel displayed in the center of the figure is originally downloaded (March 19, 2021) from the clipart-library.com, a free cliparts collection. NRF2: Nuclear factor erythroid 2-related factor 2, ARF3: AMP-dependent transcription factor 3

lipogenesis and promote adipocyte browning by inhibiting the carbohydrate-responsive element-binding protein–stearoyl-CoA desaturase-1 axis [76]. Accordingly, ATF3 is considered a therapeutic target for obesity and metabolic diseases [18,75-77]. Evidence described collectively suggest that itaconate derivatives may be used as therapeutic agents and the pathway-associated factors ATF3 and NRF2 may be served as therapeutic targets on the management of metabolic stress-associated diseases. New discoveries in this field may help the development of more effective therapeutic approach to manage stress-induced inflammation, tissue damages, and metabolic disorders.

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Conflicts of interest

Prof. Hsin-Hou Chang, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

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