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COMMENT

# Itaconate induces noncanonical AIM2-dependent PANoptosis in sepsis

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*Cellular & Molecular Immunology*; https://doi.org/10.1038/s41423-026-01428-5

Inflammation is regulated by various factors, and some regulators can play opposing roles depending on the context. One such regulator is itaconate, a mitochondrial metabolite derived from the tricarboxylic acid (TCA) cycle intermediate cis-aconitate by aconitate decarboxylase 1 (ACOD1). Until recently, itaconate has been characterized predominantly by its anti-inflammatory activity [1]. Specifically, itaconate inhibits NLR family pyrin domain containing 3 (NLRP3) inflammasome activation, activates nuclear factor erythroid 2-related factor 2 (Nrf2) to reduce oxidative stress, and blocks succinate dehydrogenase, thereby reducing proinflammatory succinate accumulation and dampening mitochondrial reactive oxygen species (ROS) production [2]. Recent studies have suggested that itaconate has dual functions in immunoregulation [3, 4]. In sepsis patients, elevated ACOD1 expression increases itaconate synthesis. It modulates cytokine production, ROS, and inflammatory factors through tumor necrosis factor-alpha-induced protein 3 (TNFAIP3) upregulation, whereas the protective effects of β-glucan are partly achieved through the suppression of ACOD1-driven itaconate accumulation. However, previous studies have not fully clarified the underlying mechanisms, and the precise molecular pathways underlying the proinflammatory effects of itaconate remain to be further explored.

Here, Ma et al. represent a significant conceptual departure from this canonical understanding, revealing the proinflammatory function of itaconate, particularly in the context of sepsis pathogenesis and PANoptosis induction [5]. The authors demonstrated that the ACOD1-itaconate pathway was robustly upregulated and that elevated itaconate levels were positively correlated with poor clinical outcomes in sepsis patients. These results suggest that itaconate can act as a driver of hyperinflammation, contributing to disease severity under specific pathophysiological conditions such as sepsis (Fig. 1). To examine the role of both endogenous and exogenous itaconate, the authors treated a cecal ligation and puncture (CLP) model with 4-octyl itaconate (4-OI), which is similar to itaconate. Compared with wild-type (WT) mice, *Acod1*$^{-/-}$ mice had a higher survival rate after CLP. However, 4-OI treatment during CLP accelerated the production of proinflammatory cytokines and decreased the survival rate. These results revealed systemic organ damage to the lung, liver and kidney with elevated levels of inflammatory markers such as MDA, leukocyte infiltration, hepatic hemorrhage, AST, ALT and BUN.

PANoptosis is an integrated inflammatory programmed cell death pathway (pyroptosis, apoptosis and necroptosis) that plays a critical role in amplifying excessive inflammation under pathological conditions through the assembly of a multiprotein complex known as the PANoptosome [6]. Previous studies have revealed that PANoptosis contributes to the pathogenesis of hyperinflammatory conditions such as sepsis. Therefore, the authors examined the induction of PANoptosis in LPS-activated macrophages, which are responsible for the activation of the innate immune response. At the cellular level, 4-OI posttreatment in LPS-primed bone marrow-derived macrophages (BMDMs) increased the secretion of proinflammatory cytokines, such as interleukin-1β and TNF-α, and induced the simultaneous activation of pyroptotic (CASP1 and GSDMD), apoptotic (CASP3 and CASP7), and necroptotic (RIPK1 and MLKL) effector molecules, which are the molecular hallmarks of PANoptosis, and the colocalization of pMLKL and cleaved CASP3 with ASC/PYCARD specks, as determined by immunofluorescence, indicating functional PANoptosome assembly [7]. Next, the authors investigated the innate immune sensor that induces PANoptosome assembly and PANoptosis, focusing on established sensors, Z-DNA binding protein 1 (ZBP1), absent in melanoma 2 (AIM2), NLRP3 and pyrin, which are encoded by the Mediterranean fever (MEFV) gene [8]. In addition, the authors focused on PYCARD/ASC oligomerization, as activated sensors recruit ASC to drive its assembly into the PANoptosome complex. Interestingly, the 4-OI-mediated increase in PYCARD-sensor interactions correlated specifically with AIM2 protein upregulation. Western blot analysis confirmed robust AIM2 expression in the LPS + 4-OI-treated cells relative to that in the LPS control cells, whereas the protein levels of the other sensors did not. Although these data, the authors confirmed that 4-OI enhances the expression of AIM2 in LPS-stimulated BMDMs, resulting in the assembly of the PANoptosome.

AIM2 is a cytosolic pattern recognition receptor that detects double-stranded DNA released during cellular stress or infection. It recognizes pathogen-associated molecular patterns from herpes simplex virus type 1 or *Francisella novicida*, oligomerizes to recruit adaptor proteins, and functions as a sensor of the PANoptosome [9]. In sepsis, PANoptosis has emerged as a critical driver of excessive inflammation, immune cell dysfunction, and multiorgan damage. Recent studies have shown that PANoptosis plays a critical role in driving the inflammatory response, impairing immune cell function, and contributing to multiorgan dysfunction in sepsis; thus, PANoptosis is emerging as a significant therapeutic target for managing sepsis [10]. Mechanistic research focuses on identifying specific molecular triggers, signaling pathways, and downstream consequences of PANoptosis activation in various organs affected by sepsis.

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Received: 28 April 2026 Accepted: 7 May 2026
Published online: 25 June 2026

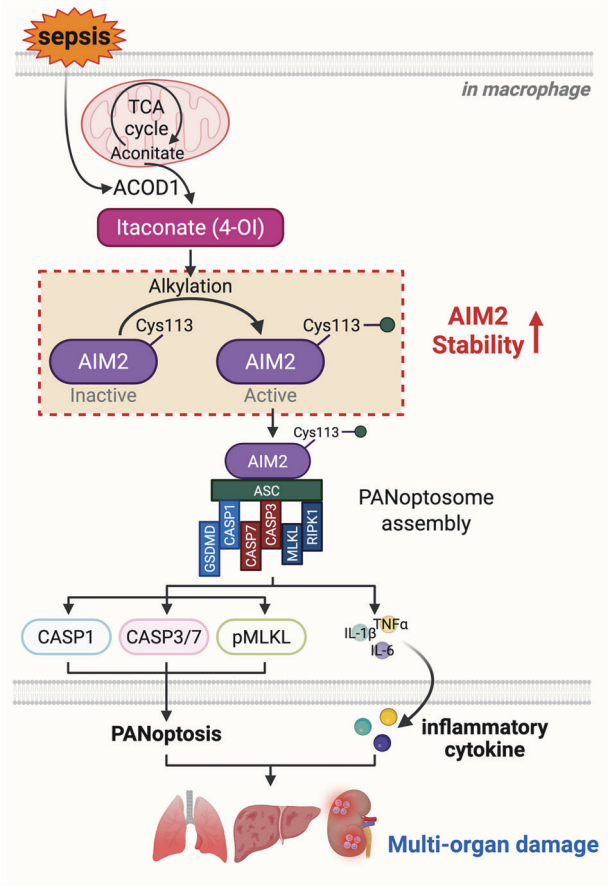


**Fig. 1 Itaconate-driven alkylation of AIM2 promotes PANoptosis and multiorgan damage during sepsis.** Activation of the ACOD1–itaconate axis increases the production of itaconate from the TCA cycle intermediate cis-aconitate. Elevated itaconate alkylates AIM2 at Cys113, facilitating the transition of AIM2 from an inactive state to an active state and promoting PANoptosome assembly. Consequently, the activation of downstream effectors of pyroptosis (CASP1), apoptosis (CASP3/7), and necroptosis (pMLKL) drives PANoptosis in macrophages. This coordinated inflammatory cell death leads to excessive cytokine release and contributes to multiorgan damage during sepsis. TCA: tricarboxylic acid, ACOD1: aconitate decarboxylase 1,4-OI: 4-octyl itaconate, AIM2: absent in melanoma 2, Cys113: cysteine at position 113, ASC: apoptosis-associated speck-like protein containing a CARD, GSDMD: gasdermin D, CASP: caspase, MLKL: mixed-lineage kinase domain-like pseudokinase, RIPK1: receptor-interacting protein kinase 1, IL: interleukin, TNFα: tumor necrosis factor alpha. This figure was created with BioRender.com

Notably, the AIM2-dependent PANoptosome assembly observed in this study represents a noncanonical activation mechanism, as it occurred independently of exogenous dsDNA, which is a well-established ligand for AIM2. Unlike the canonical AIM2 activation pathway, in which cytosolic dsDNA sensing directly triggers AIM2 inflammasome assembly, the findings suggest that other new mechanisms trigger AIM2-dependent PANpoptosis. Therefore, the authors investigated the mechanism by which AIM2 expression is elevated by 4-OI. 4-OI treatment increased AIM2 protein levels by stabilizing the protein independent of Aim2 mRNA levels. One of the functions of itaconate is alkylating cysteine residues on proteins [1]. On the basis of this feature, they hypothesized that 4-OI regulates AIM2 stability through cysteine alkylation and detected itaconate-induced alkylation in macrophages via click chemistry. By labeling cells with itaconate alkyne (ITalk), they reported 989 sites from 792 upregulated proteins that are related to the AIM2 pathway. The LC–MS/MS results also supported the docking of ITalk to a specific site, cysteine 113 (Cys133), of AIM2. This finding was further verified by the transfection of C113A-mutated AIM2 into 293 T cells, which resulted in the absence of ITalk labeling. To confirm whether the alkylation of AIM2 by itaconate induces PANoptosis, they compared PANoptosis markers in PANoptosome sensor knockout BMDMs. As a result, compared with that in WT BMDMs, the expression of PANoptosis protein markers was reduced only in *Aim2*$^{-/-}$ BMDMs. Moreover, the secretion of proinflammatory cytokines was reduced only in *Aim2*$^{-/-}$ cells compared with that in other sensor knockout cells. These findings indicate that LPS and 4-OI stimulation induce AIM2-dependent PANoptosis. Together, AIM2-dependent PANoptosome assembly induces PANoptosis and systemic inflammation in a CLP model with 4-OI treatment.

In summary, the results of this study demonstrate that excessive itaconate production acts not as an anti-inflammatory mediator but as a driver of PANoptosis and systemic organ damage during sepsis, revealing a previously unrecognized proinflammatory role. Using both murine sepsis models and patient-derived samples, the authors demonstrated that excessive ACOD1-mediated itaconate production is correlated with disease severity and mortality. Mechanistically, itaconate and its derivative 4-OI directly alkylate AIM2 at Cys113, leading to AIM2 protein stabilization through the prevention of proteasomal degradation. This post-translational modification promotes AIM2-dependent PANoptosome assembly and triggers inflammatory cell death independent of canonical ligand sensing, ultimately amplifying cytokine release, multiorgan injury, and mortality in sepsis. The key contribution of this study is the identification of a noncanonical AIM2-dependent PANoptosis activation mechanism in which a metabolic intermediate directly controls inflammasome signaling through post-translational modification rather than classical ligand-driven activation. These findings establish a fundamentally different paradigm in which metabolite-driven alkylation acts as a trigger for PANoptosis. By expanding the current understanding of PANoptosis regulation, this study identifies AIM2 as a key regulator of inflammatory signaling beyond its canonical role and highlights it as a potential therapeutic target in sepsis.

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## ACKNOWLEDGEMENTS

We thank all the members of the Lee laboratory for their comments and suggestions during the development of this manuscript. This research was supported by the Korea Drug Development Fund, funded by the Ministry of Science and ICT, Ministry of Trade, Industry and Energy, and the Ministry of Health and Welfare, Republic of Korea (RS-2025-02222987 to SL). This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Ministry of Science and ICT (MSIT) (2022R1C1C1007544, 2024M3A9H5043152 to SL), a grant from the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea under the Korea Health Technology R&D Project (RS-2025-25459955 to SL), a Research and Development (R&D) project on the animal and plant quarantine technology of the Animal and Plant Quarantine Agency in the Republic of Korea (Z-1543083-2026-29-0101 to SL), a Korean ARPA-H Project grant from the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (RS-2025-2542273 to SL), the Institute for Basic Science (IBS), Republic of Korea (IBS-R801-D9-A09, IBS-R801-D1-2025-A02, IBS-R801-D1-2026-a Additionally, research funds were granted from the Republic of Korea's National Institute of Health (Project Nos. #2025ER160200 and #2025ER240100 to SL).

## AUTHOR CONTRIBUTIONS

HK and SL conceived this study, prepared the manuscript, and critically revised and approved the final submitted version of the manuscript. All the authors contributed to the manuscript and approved the submitted version.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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