

Itaconate keeps endogenous retroviruses quiet

Carlos de la Calle Fabregat^{1#}, Javiera Villar^{1#}, Florent Ginhoux^{*1,2}

<https://doi.org/10.15302/vita.2026.09.0070>

The immuno-metabolite itaconate, which is produced by inflammatory macrophages, is identified as a direct inhibitor of the m⁶A RNA demethylase ALKBH5. By preserving m⁶A modification on endogenous retrovirus RNA transcripts, itaconate promotes their degradation and restrains type I interferon signaling, constituting a metabolic safeguard against chronic inflammation¹.

Endogenous retroviruses (ERVs) represent a major fraction of mammalian genomes; however, they are normally kept transcriptionally silent. Immune activation induces chromatin remodeling, which licenses the transcription of previously silenced ERVs. The resulting ERV-derived nucleic acids drive sustained type I interferon production and tissue-damaging inflammation. Upon inflammatory activation, macrophages also mount regulatory responses through extensive transcriptional and metabolic reprogramming. However, the regulation of retroelement expression during this process remains unclear. Here, Huang and colleagues¹ uncovered a molecular safeguard of pathogenic inflammation by modulating ERV expression through metabolic regulation. They show that itaconic acid (ITA), produced by the enzyme IRG1 (encoded by *ACOD1*), directly inhibits the RNA demethylase ALKBH5 activity through competitive displacement of α -ketoglutarate (α -KG). As a result, ERV transcripts preserve the N⁶-methyladenosine (m⁶A) modification, which promotes their degradation and prevents the accumulation of immunostimulatory retroviral nucleic acids (Fig. 1). The work identifies an IRG1-ITA-ALKBH5 axis that limits the transition from acute immune activation to chronic inflammation.

Itaconate is a known regulator of macrophage activation. Typically associated with anti-inflammatory effects, its reported actions include inhibiting succinate dehydrogenase (SDH), limiting IL-1 β production, activating NRF2 to induce antioxidant responses, restraining aerobic glycolysis, and dampening TLR-driven secondary responses². Importantly, ITA acts as a structural analogue of α -KG and has been shown to compete for the active site of α -KG-dependent enzymes, the TET DNA dioxygenases being the best-characterized example³. This finding previously identified ITA as a metabolic-epigenetic mediator, restraining TET2-dependent reprogramming associated with the macrophage pro-inflammatory program.

The present study extends ITA's functional repertoire to the regulation of endogenous retroviruses. The authors found that, following inflammatory stimulation, murine bone

marrow-derived macrophages accumulated transcripts from several ERV families, notably of intracisternal A-particle elements (IAPs). This induction, already present in wild-type cells, was markedly amplified in *Irg1*-deficient macrophages, placing IRG1 as a negative regulator of ERVs. A similar relationship was observed in human macrophages, where depletion of *IRG1* boosted levels of HERVK under LPS.

ERV expression is classically known to be controlled by epigenetic and transcriptional regulatory mechanisms⁴. Accordingly, the authors first examined chromatin, but ATAC-seq revealed no differences between *Irg1*-KO and wild-type macrophages, indicating that the chromatin opening that accompanies activation proceeds independently of ITA. The effect was likewise independent of TET2, previously known to be inhibited by ITA³. Next, they applied nascent RNA sequencing on the same setup, also with no impact on transcriptional induction of repetitive RNAs. Instead, the higher ERV amounts were explained by an increased half-life of their RNAs. Interestingly, this increased stability was associated with a loss of m⁶A, an epitranscriptomic mark which had previously been described to target ERVs for degradation⁵. To identify the link between ITA and m⁶A, the authors performed protein pull-downs against ITA, which allowed them to identify the RNA m⁶A demethylase ALKBH5. Importantly, removing *Alkbh5* from macrophages produced a destabilization of ERV transcripts even in the absence of ITA, and rendered them resistant to ITA supplementation. Finally, they selectively knocked down m⁶A RNA reader enzymes, finding YTHDF2 as a specific degrader of methylated ERV RNAs, identifying a novel IRG1-ITA-ALKBH5-YTHDF2 axis that mediates ERV transcript degradation in macrophages.

At the biochemical level, the authors demonstrated, by using *in vitro* assays with purified enzymes, that ITA directly inhibits ALKBH5 at concentrations several-fold below those it reaches in LPS-stimulated macrophages. Interestingly, inhibition by ITA was demonstrated to be specific to ALKBH5, as FTO, a related α -KG-dependent m⁶A demethylase⁶, was unaffected. The interaction between ITA and ALKBH5 was elegantly resolved by a co-crystal structure, revealing that ITA sits in the catalytic pocket, engaging key active-site residues. ITA binds ALKBH5 with an affinity comparable to that of α -KG, and an excess α -KG reversed inhibition, establishing substrate competition. Thus, ITA can function as a structurally selective regulator of an RNA-modifying enzyme.

This pathway also offers an interesting temporal perspective on the role of type I interferon in macrophage activation.

1. Université Paris-Saclay, Gustave Roussy, U1356 Next Generation Immuno-Oncology Research, Villejuif, France. 2. Shanghai Institute of Immunology, Department of Immunology and Microbiology, and Center for Human Translational Immunology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [#]These authors contributed equally.

*Correspondence: Florent Ginhoux (florent.ginhoux@gustaveroussy.fr)

Published: October 22, 2026

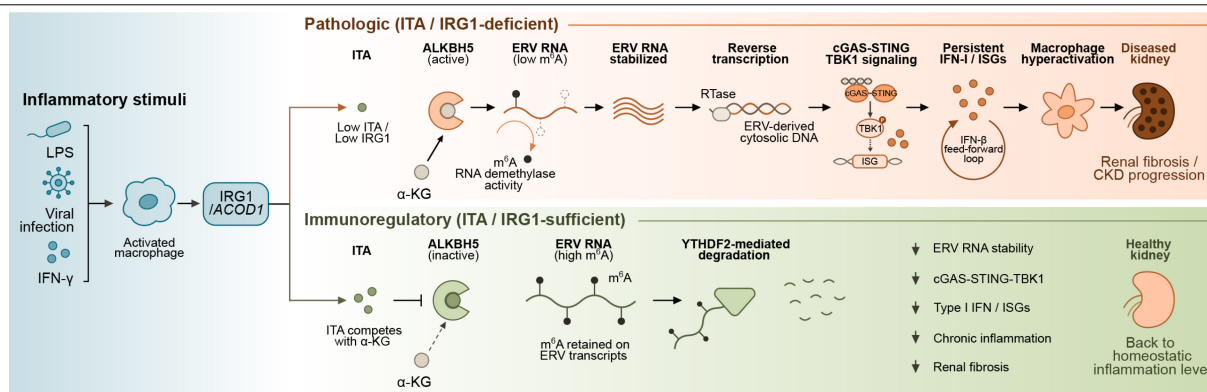


Fig. 1 Itaconate couples macrophage immunometabolism to ERV silencing. In ITA-sufficient macrophages, IRG1-derived itaconate competes with α -KG at the m⁶A demethylase ALKBH5, so m⁶A marks are retained on ERV transcripts and the RNA is cleared by YTHDF2-mediated decay, limiting cGAS-STING-TBK1 signaling and type I interferon response. When itaconate is low, ALKBH5 stays active, ERV RNA is demethylated and stabilized, and its reverse-transcribed cytosolic DNA sustains an IFN- β feed-forward loop that drives macrophage hyperactivation, renal fibrosis and chronic kidney disease (CKD) progression.

IRG1 has previously been linked to early type I interferon responses⁷, yet the present study shows that its absence causes prolonged interferon signaling at later stages of macrophage activation. ERV transcripts in *Irg1*-deficient cells are reverse transcribed into DNA and accumulate in the cytosol, and that DNA rather than the RNA itself (MAVS depletion showed no effect) triggers cGAS-STING-dependent interferon responses, creating a feed-forward loop through IFN- β production. This late IFN- β production in *Irg1*-deficient cells is suppressed following reverse transcriptase inhibition or loss of cGAS. IRG1 may therefore have different functions across the macrophage activation trajectory: supporting aspects of the initial antimicrobial response while preventing endogenous retroelements from converting a transient response into chronic inflammation.

The physiological relevance of this mechanism is illustrated in kidney disease, a condition that was previously associated with ERV dysregulation⁸. In renal biopsies from patients with IgA nephropathy, macrophage IRG1 expression inversely correlated with HERVK abundance and positively correlated with kidney function. Myeloid-specific loss of *Irg1* in mice aggravated ERV activation, type I interferon signaling, and fibrosis in two mouse models of kidney injury. Importantly, inhibition of retroviral reverse transcription alleviated disease, suggesting that ERV activity directly contributes to disease progression. ITA administration reduced ERV expression and renal fibrosis, whereas this protection disappeared when *Alkbh5* was deleted in myeloid cells, genetically connecting the therapeutic effect of ITA to its newly identified target.

Several questions now emerge. What is the relative contribution of ITA's epigenetic³ versus RNA-centered effects to its anti-inflammatory function? Which physiological conditions render the IRG1-ITA-ALKBH5 axis insufficient to restrain ERV-driven inflammation? How broadly does the pathway operate across human ERV families, which differ substantially from the highly active murine IAP elements observed in this

study? It will also be important to define when suppressing ERVs is beneficial, as controlled viral mimicry can contribute to antiviral and antitumor immunity, and also if this pathway can be modulated in humans *in vivo*.

More broadly, this study reframes the role of itaconate as more than a brake on inflammatory signaling. It reveals a novel mechanism by which metabolic reprogramming allows activated macrophages to control their own genomic remnants. By coupling an inflammation-induced metabolite to RNA modification and retroelement clearance, the proposed axis provides a mechanism by which macrophages can mount a strong response without allowing the molecular relics of the genome to maintain the response permanently switched on.

COMPETING INTERESTS

The authors declare no competing interests.

REFERENCES

- Huang, X. et al. *Vita* <https://doi.org/10.15302/vita.2026.07.0060> (2026).
- O'Neill, L.A.J. & Artyomov, M.N. *Nat. Rev. Immunol.* **19**, 273–281 (2019).
- Chen, L.L. et al. *Nat. Cell Biol.* **24**, 353–363 (2022).
- Karimi, M.M. et al. *Cell Stem Cell* **8**, 676–687 (2011).
- Chelmicki, T. et al. *Nature* **591**, 312–316 (2021).
- Jia, G.F. et al. *Nat. Chem. Biol.* **7**, 885–887 (2011).
- O'Carroll, S.M. et al. *Nat. Metab.* **6**, 2060–2069 (2024).
- Dhillon, P. et al. *Nat. Commun.* **14**, 559 (2023).

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Florent Ginhoux.

Reprints and permission information is available at <https://www.vita-journal.com/>.

© The Author(s) 2026. Published by Higher Education Press. This is an Open Access article distributed under the terms of the CC BY license (<https://creativecommons.org/licenses/by/4.0/>).