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INSIGHTS

Sticky memories of an activated macrophage

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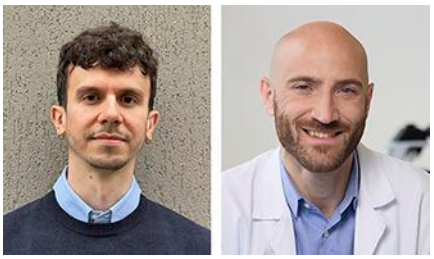
Innate immune cells can retain molecular imprints of past encounters long after the initial stimulus has ceased. In this issue, Gorin et al. (https://doi.org/10.1084/jem.20250976) reveal an unexpected mechanism by which IFN-γ sustains trained immune states through prolonged signaling driven by cytokine retention at the cell surface.

Once thought to be restricted to B and T lymphocytes, immunological memory is now recognized to also operate within the innate immune system (Netea et al., 2020). For example, macrophages exposed to the bacterial component LPS can enter a transient state of gene-specific hyporesponsiveness to subsequent challenges, a phenomenon known as endotoxin tolerance (Foster et al., 2007). In contrast, "trained immunity" (TRIM) describes the capacity of innate immune cells to mount enhanced inflammatory responses long after an acute exposure to priming stimuli, including Bacillus Calmette–Guérin (BCG), β-glucans, LPS, or inflammatory cytokines (Quintin et al., 2012). Elicitation of TRIM entails the activation (or *de novo* formation), maintenance, and recall of inflammatory gene enhancers and promoters marked by histone methylation, lactylation, and acetylation, as well as by increased chromatin accessibility (Ostuni et al., 2013; Saeed et al., 2014); these changes are fueled by products of metabolic reprogramming that act as substrates of chromatin-modifying enzymes (Ziogas et al., 2025).

TRIM operates in differentiated macrophages, whose durable persistence and limited proliferation rates in tissues enable the passive maintenance or active transmission of epigenomic memories of inflammatory challenges to drive long-term adaptations. Furthermore, hematopoietic stem and progenitor cells (HSPCs) also represent major reservoirs of TRIM, as these cells can convert inflammatory challenges into persistent chromatin states that are transmitted to their myeloid progeny (Kaufmann et al., 2018). For instance, BCG-trained HSPCs can give rise to monocytes and neutrophils with molecular and functional properties able to confer heterologous protection against unrelated infections and even cancer (Daman et al., 2025; Jurado et al., 2025). Importantly, dysregulated TRIM in HSPCs or differentiated cells has been linked to maladaptive inflammatory states underlying cardiovascular, neurodegenerative, and metabolic diseases and cancer (Hajishengallis et al., 2025), underscoring the relevance of understanding how TRIM is established, maintained, and resolved.

The prevailing model posits that TRIM is a cell-intrinsic process, whereby stimulus-induced enhancer marking is maintained or actively transmitted (via ill-defined mechanisms of epigenetic inheritance) in the absence of continued environmental stimulations. The study by Gorin et al. provides unexpected insights that might challenge this view (Gorin et al., 2026). Using a reductionist yet relevant model of human monocyte-derived macrophages stimulated acutely with IFN-γ, they found that long-term maintenance of *de novo* formed enhancers relied on continued signaling by the JAK–STAT pathway—even if the cytokine was washed out by replacing the culture medium. Inhibition of JAK1/2 with ruxolitinib in cells that were acutely stimulated with IFN-γ and later kept in fresh medium resulted in the loss of H3K4me1 and reduced chromatin accessibility at IFN-γ–induced enhancers (see panel A in figure). Removal



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of the JAK inhibitor rapidly restored STAT1 phosphorylation, indicating persistent IFN-γ signaling beyond the period of overt cytokine stimulation. Of note, transient stimulation of macrophages with LPS or type I IFN did not result in persistent STAT1 phosphorylation after washout, and this occurrence was associated with progressive loss of H3K4me1 at stimulus-induced enhancers. Gorin et al. propose membrane trapping as a driver of continued IFN-γ signaling in their experimental model, building on previous reports of this cytokine being able to bind phosphatidylserines at the plasma membrane or heparan sulfate in the extracellular matrix (ECM) (Kemna et al., 2023; Oyler-Yaniv et al., 2017). These findings suggest that, in this experimental setting (and considering possible caveats and open issues described below), maintenance of the trained state in macrophages relies on sustained signaling by retained cytokines rather than chromatin marking alone. A broader interpretation of the study is that at least some forms of TRIM may not rely entirely on cell-intrinsic transmission

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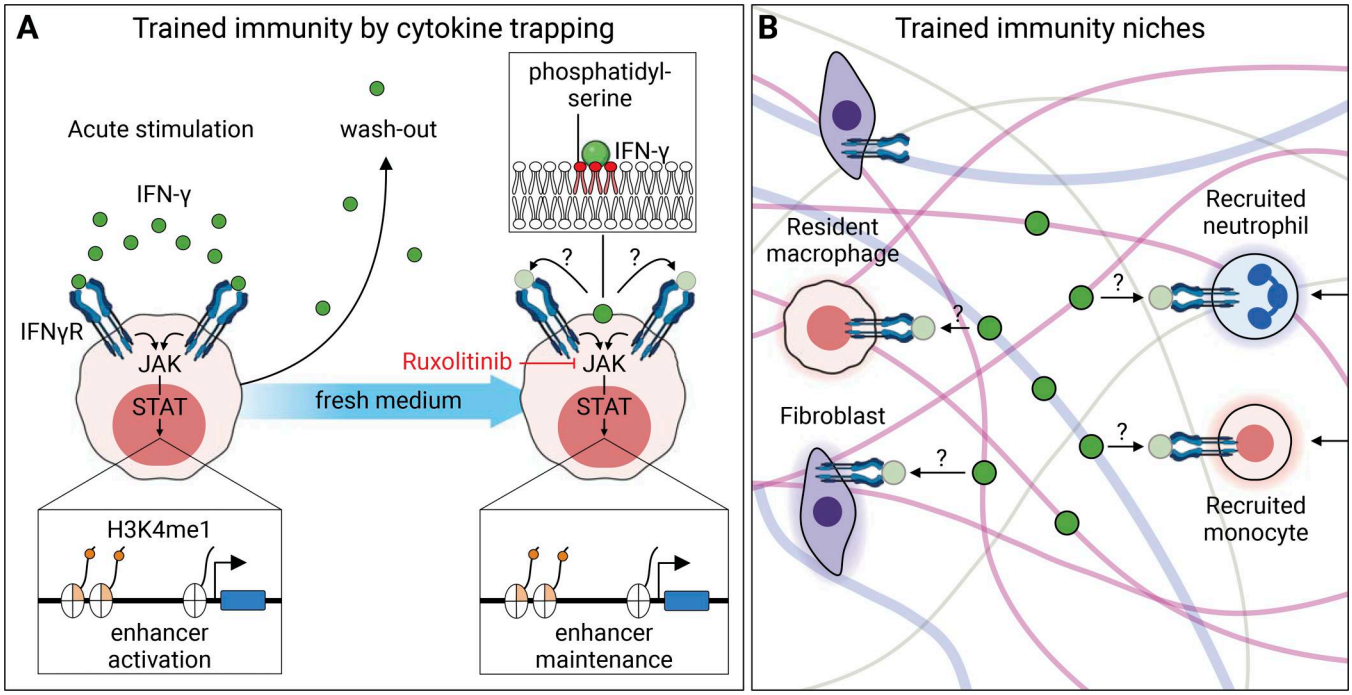

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Proposed models of cytokine-induced TRIM. (A) In acutely stimulated macrophages, binding IFN-γ to its cognate receptor IFNγR triggers JAK–STAT signaling and activation of inflammatory gene enhancers via histone methylation (left). After washout, IFN-γ is retained in the plasma membrane, possibly by exposed phosphatidylserine, thus sustaining JAK-STAT signaling and enhancer maintenance; blockade of JAK1/2 with ruxolitinib leads to loss of STAT1 phosphorylation and H3K4me1 at trained enhancers. (B) Organization of hypothetical TRIM niches *in vivo*. Locally secreted cytokines would be trapped in ECM components, including proteoglycans and protein fibers (colored lines), thus reinforcing TRIM programs in resident and newly recruited cells upon infection or damage.

of epigenetic memory but would require continued external reinforcement by cell-extrinsic cues.

Translating the observations by Gorin et al. to a theoretical *in vivo* setting, one would speculate that TRIM is not encoded exclusively within cells, but that it is also locally retained in the tissue microenvironment (see panel B in the figure). Episodes of infection or tissue damage are invariably accompanied by the local release of pathogen- or danger-associated molecules, as well as cytokines, chemokines, and metabolites that act over short distances. If these factors are retained beyond the acute phase, being trapped in plasma membranes or ECM components, they could transiently preserve information about recent immune responses within the tissue itself. In this scenario, "TRIM niches" would function as local repositories of cell-extrinsic memory, capable of reinforcing trained programs in resident cells and of transmitting them to newly recruited cells entering the site. Niche-based TRIM would be spatially heterogeneous and dynamic, reflecting variations in the cellular and extracellular composition of individual microenvironments as well as in cytokine-binding or proteolytic activities over space and time. TRIM niches would thus integrate the outcomes of cell-extrinsic reinforcements from retained stimuli with those of cell-intrinsic epigenetic inheritance, which broadly occurs in immune, stem, epithelial, and stromal cells (Ordovas-Montanes et al., 2020; Naik and Fuchs, 2022). While niche-based TRIM may be beneficial in sustaining protective immune responses, it might carry the risks of maladaptive consequences. Persistent cytokine retention could prolong inflammatory programs beyond their physiological window, contributing to chronic inflammation, fibrotic remodeling, or autoimmunity. From a therapeutic perspective, these considerations suggest that TRIM may be modulated not only at the level of immune cells but also by targeting the tissue niche by intervening on ECM components or membrane lipid composition to limit cytokine retention or promote signal clearance as strategies to reshape maladaptive immune responses.

We conclude with several cautionary notes, as the broader implications of this work rest on assumptions that are not directly addressed by the study itself. Whether cytokine retention operates in intact tissues and contributes meaningfully to TRIM *in vivo* remains to be established. Several mechanistic aspects also remain unresolved, including how trapped cytokines are released or presented to their cognate receptors, how such processes withstand proteolytic activity during macrophage activation, and whether propagation of TRIM through cell-extrinsic mechanisms requires defined quantitative thresholds of continuous or intermittent signaling. This latter point is particularly relevant given that IFN-γ signaling induces negative feedback regulators that constrain pathway activation and could therefore determine whether memory is maintained or lost (Boehmer and Zanoni, 2025). Whether stimulus trapping represents a generalizable driver of TRIM also remains an open question, as neither LPS nor type I IFN elicits persistent signaling in cultured macrophages. Similarly, it will be important to determine to what extent, if any, paradigmatic TRIM inducers such as β-glucans or BCG rely on physical persistence and/or continued signaling to elicit memory states. Even if trapping proves to be

specific to IFN-γ, the biochemical and biophysical properties that underlie this behavior remain to be defined; this would potentially inform protein design strategies to engineer longer-acting cytokines able to elicit TRIM or, alternatively, target maladaptive TRIM. Finally, while the authors carefully control for multiple variables and demonstrate the robustness of their findings across different experimental conditions, some intrinsic limitations of reductionist *in vitro* systems cannot be fully excluded. In particular, variability in the purity and composition of cytokine preparations across batches may influence biological outcomes. At the same time, the study by Gorin et al. illustrates how carefully designed, mechanistic experiments in simplified experimental settings can uncover previously unappreciated layers of immune regulation and open new directions for understanding how innate immune memory is generated and sustained. In this context, TRIM emerges as a fundamental process with far-reaching biological and therapeutic implications, whose invesigation continues to reveal unexpected complexity.

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