Rethinking 30 Years of STAT Signaling: A Threonine Switch in STAT1 Reveals Novel Protective Roles in Intestinal Inflammation

Keywords: threonine phosphorylation | Stat1 | interferons | integrins | gut epithelium

Inflammation is a double-edged sword—essential for protecting the body and promoting healing, yet potentially harmful when left unchecked. From heart disease and cancer to diabetes, Alzheimer's, and gut disorders such as inflammatory bowel disease (IBD), dysregulated inflammation lies at the core of many of today's most burdensome health conditions. A deeper understanding of how inflammatory responses are fine-tuned at the cellular level is critical for developing more precise and effective therapies.

For over than 30 years, STAT1 has been best known for its activation through tyrosine phosphorylation (Tyr701) in response to interferons, primarily mediating antiviral defense. In our recent *PNAS* study, we identified a novel phosphorylation site—**threonine 748 (Thr748)**—on the immune signaling protein **STAT1**, acting as an evolutionarily selected regulatory "switch" within epithelial cells. Our findings demonstrate that Thr748 phosphorylation acts independently of the canonical Tyr701 site to enhance epithelial resilience during inflammatory stress, such as colitis-induced tissue injury. Using intestinal epithelial cells and in vivo models of colitis, we showed that Thr748 phosphorylation upregulates key cytoskeletal and extracellular matrix genes, thereby strengthening barrier stability and protecting against interferon-induced cytotoxicity.

This work challenges the classical view of STAT1 as a simple on/off switch controlled solely by JAK-mediated tyrosine phosphorylation. Instead, we reveal that STAT1 exhibits both natural and synthetic modularity and plasticity, integrating distinct phosphorylation inputs—such as Thr748—to orchestrate context-specific cellular responses. By uncovering this previously unappreciated layer of STAT1 regulation, our study opens new therapeutic avenues aimed at selectively reinforcing epithelial barrier function without the broad immune suppression associated with current treatments.

Journal: *Proceedings of the National Academy of Sciences USA (PNAS).* July 22, 2025, online

Title: "Threonine phosphorylation of STAT1 safeguards gut epithelial integrity and restricts interferon-mediated cytotoxicity."

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www.pnas.org/doi/10.1073/pnas.2511957122

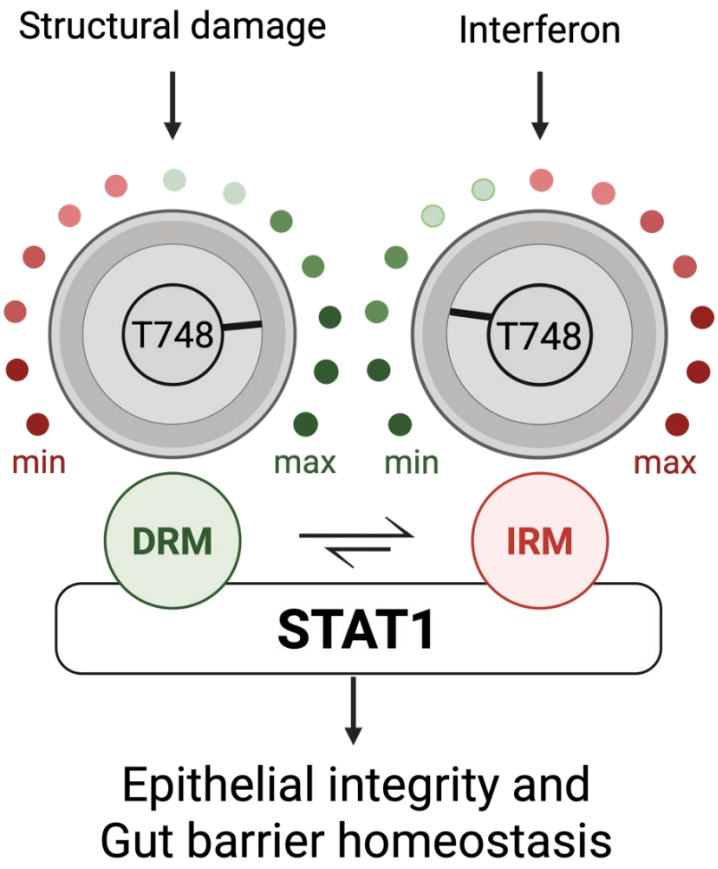

Fig. Schematic of modular STAT1 signaling architecture. Thr748 phosphorylation drives the damage-responsive module (DRM), while Tyr701 phosphorylation activates the interferon-responsive module (IRM). The dynamic balance between these two arms constitutes a phosphorylation-dependent rheostat that regulates epithelial responses and barrier function.