RESEARCH HIGHLIGHT

Metabolite is a part of immune-regulating circuit

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Metabolites play a critical role in regulating cell signaling by interacting with proteins either noncovalently or covalently, with spontaneous modifications being less understood. In a recent *Cell Research* study, Zhao et al. report that the accumulation of *S*-D-lactoylglutathione upon NF-κB activation induces spontaneous lysine D-lactylation, a process essential for maintaining immune homeostasis and appropriate host defense.

Metabolic reprogramming, such as the shift from oxidative phosphorylation to glycolysis in macrophages to support energy needs and cytokine production,[1] happens during inflammation. Metabolites like succinate and lactate function as signaling molecules, modulating immune responses and inflammation.[2,3] Moreover, immune cells can sense changes in nutrient availability, thereby linking metabolic status to immune function.[4] While it is well-established that metabolites regulate immune signaling, the question of whether immune signaling influences metabolism remains interesting.

In the current issue, Zhao et al. identified that NF-κB signaling has the ability to regulate the glycolysis branching pathway.[5] They observed a significant decrease in the mRNA and protein levels of glyoxalase II (GLO2) following bacterial and viral infections. This downregulation was controlled by tristetraprolin (TTP), an RNA-binding protein that binds to the AU-rich element in the GLO2 mRNA 3′-UTR upon inflammatory stimulation, which directly targets GLO2 mRNA and leads to GLO2 mRNA degradation. These observations revealed a novel mechanism of immune signaling to regulate metabolism.

GLO2, encoded by the hydroxyacylglutathione hydrolase (*HAGH*) gene, is a key enzyme in the glyoxalase system that catalyzes the conversion of *S*-D-lactoylglutathione (SLG) to D-lactate. Inhibition of GLO2 expression led to the intracellular accumulation of SLG, which spontaneously induced protein lysine D-lactylation within cells. D-lactylation of proteins, particularly inflammation mediators, serves as a regulatory mechanism to dampen inflammatory signaling and immune activation. The authors showed that the lysine residue K310 on RelA (p65) was a target for D-lactylation induced by SLG, which occurred in response to inflammatory stimulation, such as vesicular stomatitis virus (VSV) or lipopolysaccharide (LPS) challenge. Functionally, D-lactylation of RelA at K310 enhanced its association with IκB, an inhibitory protein that sequesters NF-κB in the cytoplasm. This interaction was critical for regulating the translocation of RelA into the nucleus, where it can modulate the transcription of genes that are involved in inflammation. Furthermore, chromatin immunoprecipitation results demonstrated that D-lactylation of RelA at K310 decreased its binding affinity to target gene promoters. In contrast, a loss-of-lactylation mutant (K310R) showed stronger binding to these promoters and increased transcriptional activity, suggesting that D-lactylation suppresses RelA's transcriptional function and, consequently, NF-κB activation. These findings illustrated that NF-κB activation-driven D-lactylation functions as a regulatory feedback mechanism that dampens inflammatory signaling and helps constrain the immune response, preventing excessive inflammation and maintaining immune homeostasis.

The authors further validated the role of GLO2 and D-lactylation in modulating inflammatory responses and immunopathology. Tamoxifen-induced *Hagh* deficient mice (*Hagh*$^{-/-}$) and their wild-type counterparts were used to assess the effects of GLO2 manipulation during viral and bacterial challenges. After intraperitoneal injections of VSV or LPS, *Hagh* deficient mice exhibited altered cytokine profiles compared to control mice, confirming that GLO2 plays a critical role in regulating immune responses during infections. Moreover, pharmacological inhibition using a selective GLO2 inhibitor DiFMOC-G in mouse models of acute inflammation and cytokine storms resulted in altered cytokine levels and improved survival rates.

Overall, this study reveals that NF-κB signaling is a direct regulator of metabolite SLG, which modifies proteins according to the law of mass action to provide a feedback regulation of NF-κB signaling (Fig. 1). SLG-induced D-lactylation is potentially targetable for inflammation-related conditions. However, several questions remian following these groundbreaking findings. For example, TTP is also known to participate in feedback regulation by destabilizing the mRNAs of a specific subset of proinflammatory cytokines and chemokines, including TNF-α, IL-1β, IL-6, and CXCL1.[6,7] It is interesting to demonstrate whether the binding motif or the secondary structure of the GLO2 mRNA 3′-UTR recognized by TTP is shared with other pro-inflammatory cytokines. This is a crucial question, as answering it could shed light on how immune responses and metabolism are orchestrated during inflammation. Moreover, this study opens opportunities for further research for other SLG-regulated mechanisms that potentially modulate inflammatory response, whether originating from inflammatory signaling, or metabolic pathways.

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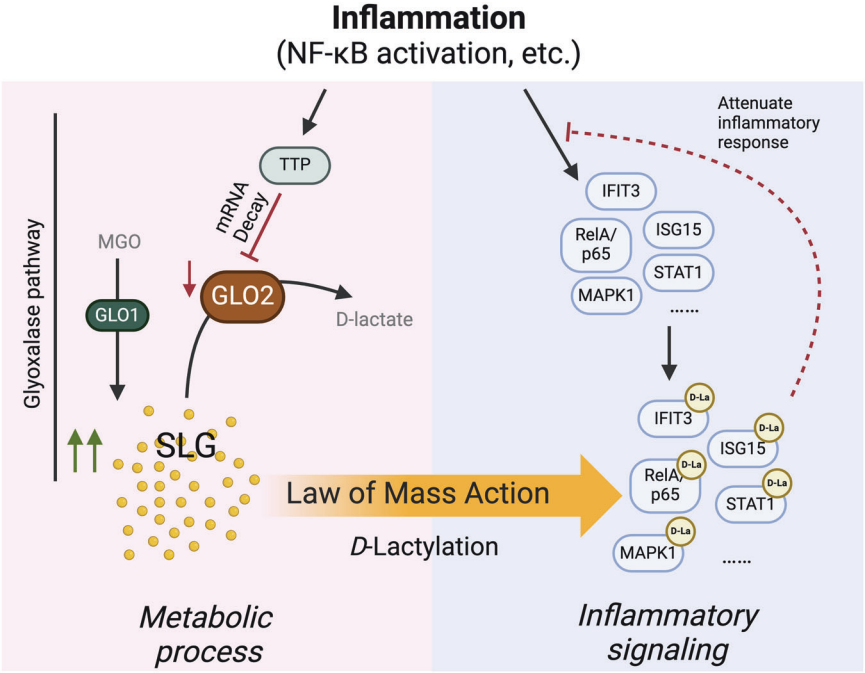

Fig. 1 Metabolic process and inflammatory signaling are orchestrated during inflammation via SLG-induced lysine D-lactylation. Inflammatory signaling triggered TTP-dependent mRNA decay of GLO2, resulting in intracellular accumulation of SLG. By the law of mass action, accumulated SLG spontaneously induces the D-lactylation of proteins that are involved in inflammatory responses, which in turn feeds back to attenuate inflammatory response, thereby maintaining a proper immune activation. TTP tristetraprolin, MGO methylglyoxal, SLG *S*-D-lactoylglutathione, IFIT3 interferon induced protein with tetratricopeptide repeats 3, ISG15 interferon-induced 15 kDa protein, MAPK1 mitogen-activated protein kinase 1, STAT1 signal transducer and activator of transcription 1.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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