Dear Editor,

Systemic inflammatory response syndrome (SIRS) and sepsis are acute inflammatory conditions that affect millions of people each year worldwide, causing tissue damage, organ failure, and even death. Early lines of evidence indicate that the exaggerated inflammatory response characteristic of SIRS and sepsis is mediated by the innate immune system. As previous studies have shown innate immune responses to be regulated by cell-intrinsic metabolism, Ma et al. examined the metabolic profiles of bone marrow derived macrophages (BMDMs) during acute inflammation in the recent issue of *Nature Communications*. Surprisingly, the authors found a strong upregulation of glycogen metabolism, consistent with a recent study that implicated glycogen as being vital for dendritic cell effector function.

Using three different murine models of acute inflammation—peritonitis, hepatitis, and sepsis—the authors show overall survival increases upwards of 50% in mice treated with pharmacological inhibitors of glycogenolysis (glycogen catabolism) or the pentose phosphate pathway (PPP). They reproduce this significantly improved survival in the same murine models with a genetic knockout of the purinergic receptor P2Y<sub>14</sub>. Using patient-derived innate immune cells from patients with SIRS or sepsis, the authors demonstrate reduced inflammatory gene expression with pharmacological inhibition of glycogenolysis or the PPP. In the same cells, they also replicate the decrease in inflammatory gene expression with genetic inhibition of the P2Y<sub>14</sub> receptor. These promising in vivo findings offer three potential targets for anti-inflammatory therapeutic intervention.

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**Abstract**

How glycogen metabolism directly regulates macrophages in the acute inflammatory state is not well understood. In the recent issue of *Nature Communications*, Ma et al. provide new insight into this process, demonstrating that glycogenolysis-driven pentose phosphate pathway and UDP-glucose-driven P2Y<sub>14</sub> receptor promote an inflammatory phenotype in macrophages. They show that in vivo blockade of glycogenolysis is sufficient to rescue survival in peritonitis, hepatitis, and sepsis. Their results hold implications for the treatment of acute inflammatory disorders at large.

**Keywords**

acute inflammation, glycogen metabolism, innate immunity

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**On the promise of glycogen phosphorylase inhibition in acute inflammation**

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in acute inflammatory disorders—glycogenolysis, the PPP, and the P2Y14 receptor—all three of which the authors implicate in the propagation of excessive and harmful inflammation.

Ma et al.³ show a striking upregulation of inflammatory gene expression in mouse BMDMs with exogenous supplementation of 200 μM UDP-glucose (UDPG), an intermediate in glycogen synthesis. Previous studies have separately established UDPG as a sugar that is shuttled out of the cell by the Golgi and as a ligand of the P2Y14 receptor in promoting pro-inflammatory signal transduction.⁴ Therefore, the authors postulate that in an acute inflammatory state, BMDMs produce elevated levels of intracellular UDPG, which is then shuttled out of the cell to bind to the P2Y14 receptor and increase pro-inflammatory signal transduction. However, there remains uncertainty as to whether BMDMs truly upregulate endogenous production of UDPG and whether the elevated levels of intracellular UDPG shuttled out do indeed increase P2Y14 receptor activation.

Glycogenolysis, the other half of glycogen metabolism, and the PPP are also implicated by Ma et al.³ in the regulation of acute inflammation. Again, using BMDMs, they demonstrate clear connections between glycogen metabolism and the PPP by genetically inhibiting glycogenolysis, and showing an increase in reactive oxygen species (ROS), a sign of PPP disruption which usually causes cell death due to oxidative overload. Intriguingly, the authors find that inhibition of glycogenolysis also downregulates inflammatory gene expression in these cells. Earlier studies have established that ROS production is generally upregulated in the inflammatory state.⁵ It remains unclear how the BMDMs concurrently find themselves in a state of oxidative stress and suppressed inflammatory gene expression. Regardless, this study offers great promise for the future of acute inflammatory disorder therapy by implicating glycogen metabolism as a clinical pharmacological target.

By inhibiting glycogen phosphorylase, the rate-limiting enzyme of glycogenolysis, Ma et al.³ elegantly show increased survival in mouse models of sepsis and decreased inflammatory gene expression in macrophages of patients with sepsis. Interestingly, additional studies have demonstrated that the inhibition of glycogen phosphorylase improves beta cell function in an obesity-induced diabetes model, suggesting glycogen phosphorylase inhibitors (GPIs) as a novel therapeutic intervention for diabetic beta cell dysfunction. GPIs were reported as having induced insulin receptor autophosphorylation, thereby leading to the activation of PI3K and mechanistic target of rapamycin complex 1 and 2 (mTORC1 and 2). mTORC, in turn, phosphorylated Akt and ribosomal protein S6 kinase beta-1 (p70S6K), contributing to the stabilization and activation of pancreatic and duodenal homeobox 1 (PDX1), an essential component of beta cell survival and growth.⁶ While glycogen phosphorylase is a logical therapeutic target for metabolic modulation of innate immune cells, delivering it solely to immune cells will remain challenging in septic patients. Pharmacological inhibition of glycogenolysis in skeletal muscle and liver would be detrimental to their normal physiologic functions. To prevent this, GPIs could be administered via novel nanoparticle and oligopeptide vector drug delivery systems trophic for macrophages specifically, reducing the likelihood of non-specific glycogen phosphorylase inhibition.⁷

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