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EDITORIAL

Tilting the Scales: Sirtuin 1 Favors Proinflammatory Macrophage Response Via Inflammasome Signaling and Metabolic Reprogramming

Sustained inflammation causes chronic liver injury, including primary sclerosing cholangitis and primary biliary cholangitis, and can be provoked by the accumulation of dying cells, translocation of bacterial products from the gut, and the accumulation of macrophages.[1] Macrophage scavenging of cellular debris is the first line of defense against hepatic injury, but macrophage activation in response to paracrine signaling is complex and has been shown to protect against but also aggravate inflammation during liver disease.[2] Therefore, understanding macrophage functions is key to defining on the molecular level their contribution to pathogenesis.

Metabolic rewiring of macrophages is a regulator of macrophage response and function following activation.[3] Indeed, a malfunctioning tricarboxylic acid (TCA) cycle enhances succinate levels that in turn promote interleukin-1β expression, which is a proinflammatory marker in macrophages.[4] Increased reliance on glycolysis activates the NLRP3-dependent inflammasome response and thus promotes macrophage activation,[3] and inflammasome activation intersects with autophagy to modulate the macrophage response. More recently, the histone deacetylase Sirtuin 1 (SIRT1) emerged as a regulator of cellular metabolism and hepatic inflammation,[5] showing that this enzyme may be signaling inflammatory events in macrophages.

In the manuscript by Isaacs-Ten et al[6] published in the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, the authors define the role of SIRT1 on macrophage activation through the regulation of cell metabolism, autophagy, and inflammasome activity in response to cholestatic injury. Furthermore, the authors examine these processes in the context of gut microbiota-derived metabolites (ie, endotoxins). Overall, the authors demonstrate that SIRT1 activity in macrophages is a key contributor to liver inflammation and fibrosis in cholestatic liver injury.

Using SIRT1-overexpressing (SIRT1^{oe}) mice, the authors noted that at basal levels this model exhibited enhanced inflammation and high hepatic macrophage density. When subjected to bile duct ligation to induce cholestasis, these phenotypes were further increased when compared with bile duct ligated mice. Bile duct ligated SIRT1^{oe} mice displayed inflammasome activation in macrophages that expressed proinflammatory and anti-inflammatory markers, demonstrating that macrophage plasticity expands beyond the simple definitions of M1 and M2 phenotypes.

Bile duct ligated SIRT1^{oe} mice had increased endotoxin translocation to the liver compared with control animals. The authors hypothesized that gut bacteria–derived factors promote macrophage activation and treated control and SIRT1^{oe} mice with lipopolysaccharide (LPS)/D-galactosamine (GalN) to address this question. SIRT1^{oe}+LPS/GalN mice displayed pronounced inflammation and increased macrophage number compared with wild-type mice treated with LPS/GalN. Confirming their hypothesis, SIRT1^{oe}+LPS/GalN mice exhibited enhanced inflammasome activation in macrophages compared with control mice treated with LPS/GalN, with little effect on hepatocyte death, showing that gut-derived endotoxin can cooperate with SIRT1 overexpression to induce macrophage activation.

The authors isolated bone marrow–derived macrophages from wild-type and SIRT1^{oe} mice and found that LPS stimulation enhanced inflammation and inflammasome activation in SIRT1^{oe} bone marrow–derived macrophages compared with control mice, and this was attributed to increased mammalian target of rapamycin complex 1 (mTORC1) signaling. LPS significantly impaired autophagy and autophagic flux in SIRT1^{oe} bone marrow–derived macrophages compared with control mice, which was further linked with mTORC1 signaling. These elegant *in vitro* results verified that SIRT1 activates the inflammasome in macrophages via mTORC1-dependent attenuation of autophagy.

When analyzing cellular metabolism, Isaacs-Ten et al[6] noted that SIRT1^{oe} bone marrow–derived macrophages treated with LPS had increased TCA cycle–related metabolites (ie, citrate, itaconate, succinate, and malate), and intriguingly the levels of itaconate and malate were increased in unstimulated SIRT1^{oe} bone marrow–derived macrophages. Additionally, stable isotype labeling in the presence of a glucose tracer demonstrated that SIRT1^{oe} bone marrow–derived macrophages treated with LPS had increased glycolytic flux compared with control mice. Remarkably, TCA cycle activity was reduced in wild-type bone marrow–derived macrophages following LPS treatment, and further decreased in LPS-treated SIRT1^{oe} bone marrow–derived macrophages.

Lastly, the authors isolated myeloid cells from wild-type or SIRT1^{oe} mice and adoptively transferred them to B6.SJL-*Ptprc*^{a} *Pepc*^{b}/BoyJ (termed PEPC) recipient mice that were subjected to bile duct ligation. PEPC mice are commonly used for cell transfer studies because they express the CD45.1, whereas wild-type mice from inbred strains express CD45.2. This allows for confirmation of donor engraftment because PEPC mice express CD45.1 on myeloid cells, whereas donor cells express CD45.2. Bile duct ligated

PEPC+SIRT1^{oe} mice had wider areas of necrosis, ductular reaction, and fibrosis compared with BDL PEPC+WT mice. In concordance with the hypothesis, macrophage inflammasome activation was enhanced in bile duct ligated PEPC+SIRT1^{oe} mice compared with bile duct ligated PEPC+WT mice. These findings conclude that myeloid cells overexpressing SIRT1 contribute to cholestatic damage via inflammasome activation and subsequent aggravation of injury.

In sum, this study defines the role of SIRT1 overexpression in macrophages during cholestasis. The authors define the impact of endotoxin signaling on SIRT1-dependent inflammasome activation, changes in cell metabolism, and the subsequent hepatic fibroinflammatory response during cholestasis. These further the understanding of and continue to define the complicated response of macrophages during liver damage.

Although the authors focus on the impact of SIRT1 overexpression in macrophages, an important limitation of their study is the use of whole body SIRT1^{oe} expressing mice. Therefore, SIRT1 signaling in other cells may have contributed to some of the observed phenotypes. This is important to note because enhanced hepatic SIRT1 expression is found in human primary biliary cholangitis and primary sclerosing cholangitis.[5]

Although proinflammatory and anti-inflammatory properties of macrophages contribute to different liver diseases, this paper points toward a proinflammatory and damaging role for macrophages in models of obstructive cholestasis. Others have found SIRT1 to be proinflammatory in liver cancer,[7] whereas macrophages have an anti-inflammatory role in fatty liver disease.[8] Thus, the inflammatory properties of macrophages are highly debated and need further clarification.

The authors mechanistically describe SIRT1 mediation of macrophage inflammation via mTORC1 signaling, inflammasome activation, and dysregulated cellular metabolism. Autophagy control of inflammasome activity has been described[9] and parallels other work wherein mTOR inhibited autophagy during tumor progression.[10] The finding of dysregulated cellular metabolism is novel, and the authors describe the rewiring of the macrophage TCA cycle as "analogous to the Warburg effect," which has been studied extensively in liver cancer, but not in cholestasis. The TCA cycle–related intermediates have immunomodulatory functions that promote macrophage inflammatory response[6]; therefore, the contribution of SIRT1 to metabolic rewiring would be an interesting avenue to study in other liver disorders. In sum, this paper provides novel mechanistic data to support a role for SIRT1 in the promotion of proinflammatory responses in macrophages.

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