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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Osr1 Is a Critical Regulator of Macrophage Polarization in NASH Progression

Nonalcoholic steatohepatitis (NASH) is a chronic liver disease, an aggressive form of nonalcoholic fatty liver disease (NAFLD) by the mixture of liver inflammation, steatosis, and fibrosis, that is becoming a leading cause of liver-related morbidity and mortality worldwide.[1] To reach the stage of NASH from simple steatosis, the immune cell-mediated inflammatory process is considered as a major step.[1] Since their discovery in 1876, Kupffer cells (KCs) have been identified as liver resident macrophages to preserve tissue homeostasis.[2] KCs are originated from yolk sac–derived progenitor cells, while monocyte-derived macrophages are also recruited into the liver from peripheral blood. It remains to be determined which group of macrophages is a major contributing cell type in NASH progression and what the underlying molecular mechanism is.

Macrophages are functionally dynamic with levels of plasticity. Under induction of different microenvironmental cues, macrophages can be polarized into classically activated macrophages (M1) or alternatively activated macrophages (M2). The M1 and M2 macrophages may have opposing roles in many pathophysiological processes, such as tumorigenesis, tissue repair, and metabolism in the context of diseases.[3] Despite extensive analyses of liver macrophages in steatosis and NASH for many years, it remains unclear if macrophage polarization happens due to replacing monocyte-derived macrophage for KC loss or if KCs can be easily polarized. Furthermore, it is important to determine which molecules are the intrinsic switching factor(s) to polarize macrophages in promoting NASH progression.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Liu et al[4] investigated cell type–specific odd skipped-related 1 (*Osr1*) effects in 4 different NASH mouse models. *Osr1*, a member of the OSR family, is a C2H2-containing zinc finger transcription factor that is involved in embryonic development and cancer cell proliferation.[5,6] Xie's group reported previously that the whole-body *Osr1* gene deletion promotes NASH progression in mice,[7,8] but it is unclear which type of cells was responsible for the NASH-promoting effect. This study showed that *Osr1* was highly expressed in myeloid cells compared with other cells in human livers with NASH and in mouse NASH models. Further, the authors detected high levels of *Osr1* expression in monocyte-derived macrophages (F4/80$^+$ Clec4f$^-$), which exhibited M2-like phenotypes, in methionine choline-deficient and high-fat diet models.

To decipher a cell type–specific role of *Osr1*, the authors generated mutant mouse lines with *Osr1* deleted in hepatocytes (*Osr1*$^{F/F}$:Alb-Cre) or in myeloid cells (*Osr1*$^{F/F}$:LysM-Cre) and treated the mice with methionine choline-deficient and high-fat diets. Interestingly, *Osr1* loss in myeloid cells, but not hepatocytes, promoted steatosis and hepatic inflammation for aggressive NASH development. *Osr1*-deficient macrophages were skewed to M1 macrophages secreting proinflammatory cytokines (tumor necrosis factor α and interleukin-1β). To understand if *Osr1* removal from myeloid cells facilitated the reprogramming of M1 macrophages upon stimuli, exposure to lipopolysaccharide and interleukin-4 was applied to bone marrow–derived macrophages isolated from control (*Osr1*$^{F/F}$) and *Osr1*$^{\Delta Mac}$ mice. Interestingly, *Osr1*-deficient macrophages were more responsive to lipopolysaccharide treatment; featured elevated activation of p38, JNK, and nuclear factor κB pathways; and were accompanied by an augmented expression of proinflammatory cytokines. However, bone marrow–derived macrophages isolated from *Osr1*$^{\Delta Mac}$ livers were poorly responsive to interleukin-4 exposure, suggesting that *Osr1* deficiency strongly skewed M1-like macrophages. Thus, *Osr1* is a critical transcription factor in the regulation of alternative macrophage polarization.

Given *Osr1* deletion in myeloid cells is favored toward the M1 phenotype to promote NASH progression, the authors investigated the downstream targets of *Osr1* in reprograming the macrophage phenotypes. By performing unsupervised transcriptomic analysis, the researchers identified PPARγ and Myc as potential candidates. Further investigation confirmed PPARγ and Myc as direct targets of *Osr1* by chromatin immunoprecipitation polymerase chain reaction and luciferase reporter assay in regulation of macrophage polarization. Rescuing PPARγ function by treatment of rosiglitazone, a PPARγ agonist, or exogenous expression of *Osr1*, delivered by an adeno-associated virus system, led to liver inflammation resolution and restoration of the M2-like phenotypes. These data suggest that PPARγ is a downstream target of *Osr1* in mediating macrophage polarization. Moreover, rosiglitazone treatment restored the oxygen consumption rate, featured by a decreased ratio of glycolysis vs OXPHOS in *Osr1*-deficient macrophages. Indeed, it rescued *Osr1* expression to alleviate the NAFLD/NASH symptoms and liver inflammation. *Osr1*-expressing macrophages exhibited M2-like phenotypes (F4/80$^+$Clec4f$^-$), which are not KCs. Indeed, the putative role of KCs was not explored in this study. The cellular properties of *Osr1*-deficient macrophages and the underlying molecular mechanisms in driving NASH development are not fully understood yet. Nonetheless, this study identified *Osr1* as a transcription factor that plays a critical role in the regulation of macrophage polarization. A promising therapeutic approach by targeting *Osr1*-mediated macrophages or using

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rosiglitazone for activation of the *Osr1*-PPARg axis could be beneficial for patients suffering from NAFLD/NASH.

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Conflicts of Interest
The authors disclose no conflicts.

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