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Contradiction: Inhibiting inflammation and immunosuppression in the treatment of IBD

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Recently, Hou et al. discovered that inhibiting Sirt2 enhances intestinal barrier integrity by suppressing the endocytosis of E-cadherin in Dextran Sulfate Sodium Salt (DSS)-induced colitis (DSS-colitis) (1). Interestingly, the authors also investigate the underlying reasons for the contrasting effects observed between genetic knockout and pharmacological inhibition of Sirt2 (1).

This study provides a foundation for considering the feasibility of an anti-inflammatory bowel disease (IBD) drug discovery strategy focused on enhancing mucosal barrier homeostasis and tissue repair through inhibiting Sirt2. We are privileged to offer additional considerations that will aid readers in comprehending the significance of this research.

While promoting mucosal barrier restoration is important, controlling inflammation has been confirmed as the primary and more effective approach for patients with active IBD, despite the associated increased risk of infection and tumor formation (2). Human genetic studies have indicated that less suppressive yet effective immunomodulation is possible and beneficial in treating IBD (3). There is a contradiction between inhibiting inflammation and immunosuppression in the treatment of IBD. Fig. 1 illustrates the crucial role of SIRT2 in intestinal cell differentiation and macrophage polarization, which are essential for inflammation and immune homeostasis. Genetic knockout and pharmacological inhibition of Sirt2 have distinct functions: genetic knockout may lead to immunodeficiency in mice and exacerbate colitis symptoms in DSS-colitis due to increased susceptibility of immune response to intestinal bacteria. However, Sirt2 inhibition offers protection against DSS-colitis by controlling inflammation. Similar patterns have been observed with other targets, such as TYK2 [a nonreceptor tyrosine kinase belonging to the Janus kinase (Jak) family] (4), NINJ1 (plasma-membrane protein ninjurin-1) (5, 6), and NLRP3 (a member of the domain-like receptors family, pyrin domain-containing 3) (7), among others. For instance, the divergent effects mediated by NLRP3 in DSS-colitis can be attributed to variations in DSS dosage or mouse strains (7). These findings shed light on anti-IBD drug discovery. First, as emphasized by Hou et al., there is a need to develop substrate-dependent inhibitors (1). Second, future anti-IBD drug discovery should focus on more selective targeting of specific signaling pathways against specific cytokines or inflammatory molecules, while avoiding widespread inhibitory effects on the immune system.

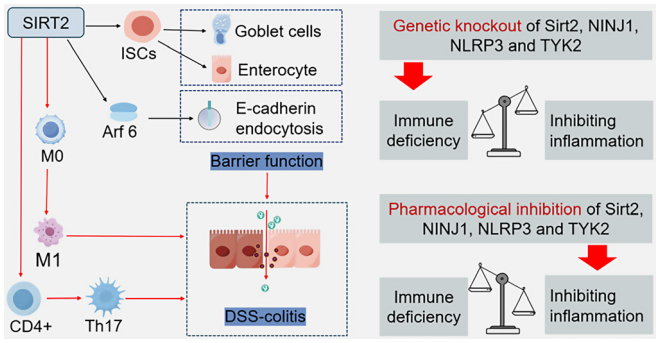

Fig. 1. The role of Sirt2 and other target proteins in intestinal inflammation and immune function.

Moreover, Hou et al. highlight the significance of adherens junctions (AJ) in the etiology of IBD. The authors demonstrate that disruption of Sirt2 inhibits the endocytosis of the AJ protein E-cadherin. Historically, our focus has primarily been on the role of tight junctions (TJ) in the onset and progression of IBD. Alterations in TJ and the associated dysfunction of the intestinal barrier have been observed in patients with active IBD (8). This discovery presents a potential novel target for restoring the intestinal barrier in IBD.

Significantly, the findings by Hou et al. provide valuable guidance for conducting more targeted research on anti-inflammatory drugs for treating IBD. However, several questions still need to be addressed. For instance, if we were to choose an animal model with a distinct pathogenic mechanism from DSS, would there be other mechanisms implicated in the regulation of IBD by Sirt2? Exploring this aspect in germfree mice or IL-10-deficient mice would be particularly intriguing.

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