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Can Rodent Model of Acetic Acid-Induced Colitis be Used to Study the Pathogenesis of Colitis-Associated Intestinal Fibrosis?

Saravanan Subramanian[1,2], **Chao Du**[1,2,3], **Xiao-Di Tan**[1,2,4]

[1]Center for Intestinal and Liver Inflammation Research, Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

[2]Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[3]Department of Gastroenterology, Linyi People's Hospital, Shandong University, Linyi, Shandong, China

[4]Department of Pathology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

Abstract

Inflammatory bowel disease (IBD) is a devastating relapsing-remitting systemic disease of the gastrointestinal system. It is characterized by an extremely imbalanced immune system and inflammatory mediators that result from the disruption of a complex series of interactions between the microbiome, the mucosal barrier, and the immune system. Over the past decades, numerous animal models such as chemical, genetic and bacterial models have populated to understanding pathophysiology of IBD and preclinical screening of therapeutic compounds for novel treatments. Among chemical-induced colitis models, the acetic-acid induced model is one of the legacy colitis models related to extensive hemorrhage, occasional ulceration, epithelium damage, and bowel wall thickening. Recently, Bahrami and his colleagues have reported the development of mucosal inflammation and intestinal fibrosis after exposure to 4% acetic acid for 10 min. Here, how their work addresses the importance of characterizing acetic-acid-induced colitis model to study the clinical features of IBD is commented.

In 1978, MacPherson and Pfeiffer performed a landmark experiment in which they administered diluted acetic acid intrarectally to rodents. They found that this approach induced mucosal inflammation and tissue damage that mimics the pathological phenotype of human ulcerative colitis (UC) [1]. Their work provided an *in vivo* tool for exploring therapeutics for inflammatory bowel disease (IBD). The popularity of this rodent model of chemical-induced colitis has diminished since the 1990's due to growing concerns that the molecular mechanisms and immunologic events leading to inflammation and mucosal injury

Corresponding author: Xiao-Di Tan, MD, Tel: 312-503-7172, Fax: 312-503-7177, xtan@northwestern.edu, Mailing Address: Ann & Robert H. Lurie Children's Hospital of Chicago, 225 E. Chicago Avenue, Box 205, Chicago, IL 60611, USA.

in human UC are very different than those in acetic acid-induced colitis [2–4]. However, this legacy rodent model remains useful for the study of pathological characteristics of human IBD and for screening drugs with anti-colitic activity. Not only is colitis easy to induce and highly reproducible in this model, but the acetic acid-induced colonic mucosal injury also bears a close resemblance to the histopathological features and inflammatory mediator profiles of the human disease [2,3].

It has been noted that recurrent episodes of intestinal inflammatory injury followed by mucosal healing can lead to intestinal fibrosis due to mucosal and submucosal deposition of extracellular matrix (ECM) [5]. Emerging evidence indicates a need for improved experimental colitis models related to bowel inflammation and fibrosis in order to expand our understanding of various pathophysiological aspects in human IBD [6]. It has been shown that rodents develop colitis after exposure of colonic mucosa to chemicals such as dextran sulfate sodium (DSS), 2, 4, 6-trinitrobenzene sulfonic acid 34 (TNBS), acetic acid, oxazolone, cartagena iodoacetamide, and indomethacin [7]. Particularly, DSS- and TNBS-induced colitis models are widely used to evaluate the factors implicated in mucosal inflammation and fibrosis during the pathogenesis of IBD and provide the opportunity to study acute and chronic mucosal repair mechanisms. The TNBS-induced model displays T-cell dependent colonic inflammation that results in Th1 to Th2 cytokine switch-mediated fibrosis [8,9], while DSS-induced colonic inflammation and its associated fibrosis are observed in T cell and B cell-deficient mice [10]. Depending on the exogenous agent used, animal models allow for the study of various molecular and cellular mechanisms of mucosal inflammation driving fibrosis and mucosal wound-healing processes associated with IBD. However, the relevance of these models to colonic inflammation and fibrosis in IBD patients still a topic of debate [11], underscoring the need for better animal models to mimic the clinical features of IBD.

In this issue of the *Journal of Investigative Surgery*, *Bahrami et al.* [12] reported on their work to improve the acetic acid-induced colitis mouse model by characterizing dynamic wound healing changes in the colonic mucosa after briefly exposing the colon to 4% acetic acid for different lengths of time. They described the onset of mucosal inflammation within 3 days and the development of bowel wall fibrosis on day 9 after exposure to 4% acetic acid for 10 min. Their study lends renewed support to the relevance of the acetic acid-induced colitis model to pathological features of human IBD and suggests that the model can be utilized to study the full pathological spectrum of human UC, ranging from mucosal inflammation to intestinal fibrosis, as well as mechanisms underlying the colonic mucosal wound-healing process. On the other hand, *Bahrami et al.* [12] did not carry out biochemical and molecular studies to confirm in detail the induction of colitis related to the duration of acetic acid contact. However, their study opens new opportunities for future investigations with this improved chemical-induced colitis model, for example, to understand the mechanisms involved in IBD-associated pathological events such as inflammatory cell infiltration, mucosal wound healing, tissue remodeling, and intestinal fibrosis. There is no doubt that rodent models of chemically induced colitis are invaluable tools for gaining fundamental insights into IBD-associated mucosal wound-healing processes and that they will continue to play a pivotal role in drug discovery and development in IBD preclinical research.

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