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Commentary

Damps' role in inflammatory bowel disease: a paradoxical player of mtDNA-STING signaling pathway in gut homeostasis

Qiongyuan Hu [a], Yanhan Ren [b], Dominic A. Slade [c], Quan Zhou [d], Xiuwen Wu [a], Jinjian Huang [a], Guosheng Gu [a,*], Gefei Wang [a,*], Jianan Ren [a,*], Jieshou Li [a,b,c,d]

[a] Research Institute of General Surgery, Jinling Hospital, School of Medicine, Nanjing University, Nanjing 210093, China
[b] Chicago Medical School, Rosalind Franklin University, North Chicago, IL 60064-3095, USA
[c] Department of Surgery, Salford Royal NHS Foundation Trust, Stott Lane, Salford, UK
[d] School of Medicine, Nanjing University, Nanjing 210029, China

The inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis, are chronic, relapsing immune mediated disorders of the gastrointestinal homeostasis and intestinal inflammation [1]. Failure to resolve mucosal inflammation and maintain gut barrier are notable shared clinical challenges in IBD management. Increasing evidence indicated that "damage associated molecular patterns" (DAMPs) as "alarmins" or "danger stimuli" can initiate and maintain mucosal inflammation in IBD, in particular when they activate immune cells within the gut lamia propria. Clinical trials and animal model studies aiming towards DAMPs have demonstrated that they can be effective therapeutic targets in mucosal inflammation of IBD. Mitochondrial DNA (mtDNA) is emerging as one of the most attractive DAMPs in promoting innate response. Hence, we highlighted the role of mtDNA in regulating gut homeostasis and mucosal inflammation in IBD in this commentary.

DAMPs are endogenous stress molecules released from tissue or cell injuries. They can induce secondary inflammation and maintain inflammatory process in IBD. The most widely accepted hypothesis underpinning the role of DAMPs in IBD involves 4 pathogenic components: promoting epigenetic reprogramming, inducing acute or chronic inflammation, damaging epithelial barrier, and disrupting mucosal microenvironment. Mitochondria is recently considered as the main source of DAMPs in IBD. Our recent results show that mitochondrial dysfunction of intestinal epithelial cells can aggravate mucosal injury and gut inflammation [2]. Among all mitochondrial DAMPs, mtDNA can lead to the strongest reaction. Just as bacterial DNA can induce immune response, mtDNA has similar immunogenic function during their uncontrolled release. It is demonstrated by Ren Lai's group that both bacterial DNA and mtDNA could be complexed with LL-37 to promote inflammation and cause localized tissue damages in mouse models with colitis and atherosclerosis [3,4].

In IBD, extensively inflamed mucosa is the source of local and systemic DAMPs. Our previous studies also indicate mtDNA released from injured IECs can mediate extensive pro-inflammatory responses via multiple pathways, notably Toll-like receptor (TLR9), inflammasome, and/or stimulator of interferon genes (STING) pathways. Boyapati et al. [5] have identified that amount of plasma mtDNA released from gut mucosa are associated with the degree of disease activity and severity. In addition, increased $TLR9^{+}$ pro-inflammatory cells in the lamina propria can be observed in active IBD. Their results point out that mtDNA-TLR9 pathway can be the potential therapeutic target in IBD. Similarly, increased plasma mtDNA level was showed in our recent CD patients ($n = 10$) compared with the healthy controls ($n = 10$) (Fig. 1a). Additionally, we discovered TLR9 expression level was significantly increased in the intestines of active CD patients. Furthermore, STING, a novel DNA sensor, was markedly elevated in the intestinal lamina propria compared to normal control (Fig. 1b). Our findings demonstrated the crucial role of mtDNA-STING signaling in gut homeostasis and intestinal inflammation in IBD.

STING is an adaptor protein that regulates innate immune response in response to bacterial components (cyclic dinucleotides and microbial DNA) and host self-DNA (nuclear DNA and mtDNA). Previous studies have indicated that STING signaling can promote intestinal homeostasis, maintain gut barrier function, and induce intestinal inflammatory response. Zhu et al. [6] demonstrated the crucial role of STING pathway in protecting against colorectal tumorigenesis via intestinal inflammation governance. Fischer et al. [7] further showed that STING signaling induces increased secretion of type I interferon, which can promote gut epithelial barrier integrity during acute intestinal injury. Just like other types of inflammation, STING pathway can act as a double-edged sword in gut pathologies. The results of Zeng et al. and our group demonstrated that the activation of STING signaling significantly aggravate intestinal pro-inflammatory injury and impairs gut barrier during sepsis [8,9]. We further showed that intraperitoneal injection of mtDNA promoted the induction of inflammatory cytokines

* Corresponding authors.
E-mail addresses: guguoshengde@163.com (G. Gu), wgfwang@gmail.com (G. Wang), JiananR@gmail.com (J. Ren).

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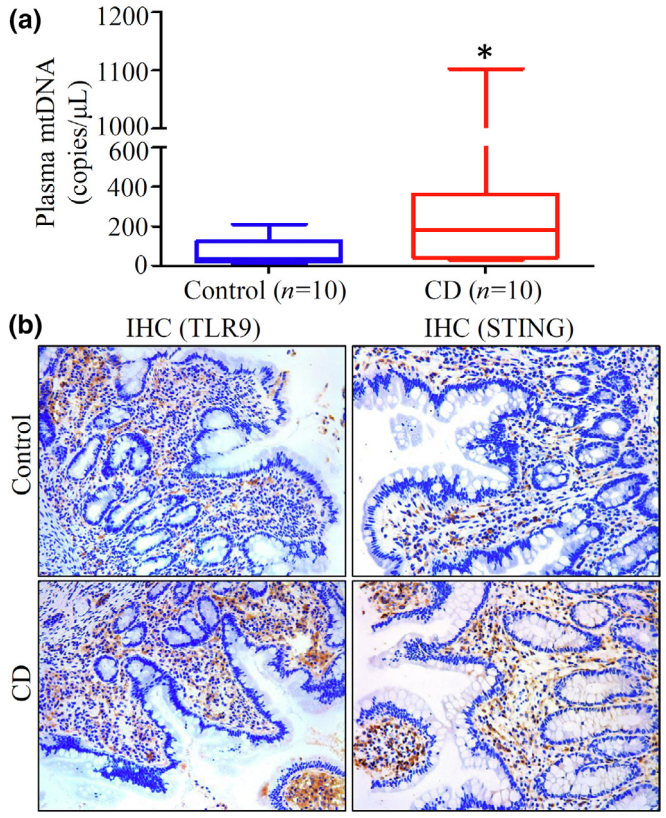

Fig. 1. (a) Plasma mtDNA level was detected using qPCR in Crohn's disease and healthy control. (b) Expression level of TLR9 and STING in human intestines were analyzed through IHC staining. For IHC, slides were treated with anti-TLR9 antibody (ab37154; Abcam), anti-STING antibody (D2P2F; 13647; Cell Signaling) according to the manufacturer's instructions. qPCR, quantitative PCR; mtDNA, mitochondrial DNA; IHC, immunohistochemistry; TLR9 (Toll-like receptor 9), STING, stimulator of interferon genes.

via STING signaling [9]. These data identify the crucial yet paradoxical roles of mtDNA-STING pathway in gut barrier maintenance.

Canesso et al. [10] proved that gut microbiota homeostasis is disrupted in mice with STING deficiency, evidenced by a reduction in the beneficial bacterium along with an increase in harmful bacteria. They showed that both STING and interferon -α/βR knockout mice are markedly susceptible to dextran sodium sulfate (DSS) and T-cell-induced colitis. Their results suggested that DNA-STING pathway may have crucial functions in controlling gut inflammation and maintaining gut barrier. At the same time, they reported that monocyte is the predominant cell type responsible for STING-mediated intestinal inflammation. Moreover, the loss of cGAS-STING signaling can protect against severe colitis induced by IL-10 deficiency [11]. Interestingly, Aden et al. [12] recently showed that IL-22 engaged cGAS/STING signaling pathway can induce a pro-inflammatory, necroptotic responses in intestinal epithelial cells and aggravate gut injury upon DSS irritant challenge. Therefore, the presented evidence indicated that STING pathway's role in regulating pathological process may arise due to a diverse set of factors and stimulations.

In our recent report, we suggested that the degree of STING activation may be associated with the process of disease [13]. Adia's laboratory recently found that STING signaling play a completely different role in pancreatitis. cGAS/STING signaling pathway in macrophages activates pancreatic inflammation and injury in acute pancreatitis [14]; however, STING activation in Th17 cells diminish the production of IL-17 and decrease chronic pancreatitis-associated inflammation and fibrosis [15]. IL-17 signaling is also crucial in shaping and regulating gut homeostasis. In our opinion, the function of STING activation in IBD may be associated with two major factors. Firstly, various inflammatory states of IBD with different degrees of STING activation may help to explain STING's role in gut immune response. Secondly, STING signaling determines the outcomes of IBD, depending on the type of immune cells involved. STING activation in innate cells may lead to induction of proinflammatory cytokines, whereas the activation in adaptive cells may be associated with anti-inflammatory response.

A number of DAMPs have been implicated in IBD. Nevertheless, the specific roles of these DAMPs require further investigation. mtDNA's activity as a DAMP is mainly derived from stressed or injured IECs, which can control the capacity of immune response in gut. In conclusion, mtDNA-STING signaling plays a paradoxical role in regulating gut homeostasis and mucosal inflammation in IBD. Therefore, further studies are needed to understand the function of mDNA-STING pathway in gut homeostasis.

Conflict of interest

The authors declare that they have no conflict of interest.

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Qiongyuan Hu is a Ph.D. candidate at Jinling Hospital, School of Medicine, Nanjing University. His research interests focus on the diagnosis and treatment of intestinal barrier in critical ill patients.

Gefei Wang, M.D. is an associate professor at Jinling Hospital, School of Medicine, Nanjing University. His research interests focus on the diagnosis and treatment of intestinal dysfunction of critical illness, intra-abdominal infection, gastrointestinal fistula, enteroatmospheric fistula of open abdomen and Crohn's disease.

Jianan Ren is the Director of Research Institute of General Surgery. His research interests focus on the diagnosis and treatment of gastrointestinal fistula and intra-abdominal infection.