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INVITED COMMENTARY

Regular or DCAF2: How CRL4^{DCAF2} Affects IBD-Related Mucosal Injury

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Cullin 4-associated factor 2 (CRL4^{DCAF2}) belongs to Cullin ring-finger ubiquitin ligases (CRLs) family of E3 ligases [1]. CRL4^{DCAF2} (referred to hereafter as DCAF2) is implicated in multiple cellular functions, including immunoregulation, transcriptional regulation, and cell cycle progression. DCAF2 ubiquitinates autophagic and apoptotic proteins, in part promoting cell proliferation by inhibiting some of the cellular programmed death pathways, including apoptosis and autophagy [2]. This function has potentially harmful consequences for cancer progression, since autophagy and apoptosis are part of immune mechanisms that curb proliferation [1]. Nevertheless, promoting proliferation can impair autoimmune inflammatory damage, even though DCAF2 activation can be protective [3] or harmful [4] in several autoimmune diseases, including inflammatory bowel disease (IBD). Thus, it is important to identify the contributions of DCAF2 to immune mechanisms in a variety of tissues and diseases.

In this issue of *Digestive Diseases and Sciences*, Zhang et al. [5] investigate the role of intestinal epithelial cells (IECs)-specific DCAF2 in maintaining intestinal homeostasis and their influence on cell cycle regulation in an animal model of IBD. For this purpose, CRL4^{DCAF2} mice with C57BL/6 background were crossed with the villin-Cre mice (C57BL6 background) to produce IEC-specific DCAF2 conditional knockout mice (termed hereafter as DCAF2^{EKD}). The simultaneously produced IEC wild-type littermates (termed hereafter as DCAF2^{EWT}) were used as controls.

Surprisingly, there was no difference observed in the growth and development between DCAF2^{EKD} and DCAF2^{EWT} mice in baseline conditions. Similarly, the conventionally stained colonic tissues in both of mouse strains showed normal epithelial cell architecture. Expression of intestinal epithelial barrier-related proteins was also similar in baseline conditions indicating the downregulation of IEC-specific DCAF2. On the contrary, global KO DCAF2 led to embryonic death which highlighted the importance of IEC-specific DCAF2 in survival of mice.

Nevertheless, when colitis was induced using dextran sodium sulfate (DSS), a significantly higher disease activity index (DAI) and mucosal damage was evident in the DCAF2^{EKD} compared with DCAF2^{WT} mice. DSS induces colitis by disrupting the colonic epithelium with associated luminal bacterial translocation, triggering an innate immune response leading to mucosal damage and subsequent colitis [6]. Colonic epithelial disruption was inferred from reduced levels of surrogate marker tight junction proteins in DCAF2^{EKD} mice compared with DCAF2^{EWT} mice, suggesting greater mucosal damage due to downregulation of DCAF2 gene. The decreased expression of these surrogate permeability markers was further correlated with a relative increase in systemic bacterial 16S RNA levels in DCAF2^{EKD} as compared with DCAF2^{EWT} mice, indicative of enhanced bacterial translocation.

The regeneration of the epithelium in response to damage is a natural immunoregulatory mechanism and can be assessed by the Ki-67 proliferative index. This index was markedly low in the DCAF^{EKD} mice as compared with DCAF2^{EWT} mice, likely rendering them less able to regenerate the colonic epithelium, consistent with a protective function of DCAF2. The authors further strengthen the argument of DCAF2 in IECs protects agonist autoimmune disease by showing upregulation of apoptosis-related molecules in the inflamed mucosa of DCAF2^{EKD} mice, also indicative of deficient mucosal repair mechanisms.

The protective function of DCAF2 has previously been reported by Huang et al. [3] who showed that loss of DCAF2 in DCs attenuated inflammation in the DC-specific DCAF2 conditional knockout mice model of psoriasis [3]. In contrast,

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Fan et al. [4] reported the loss of DCAF2 in T cells reduced the severity in an autoimmune encephalomyelitis model in a T-cell-specific DCAF2 conditional knockout mice [4].

In the current study, Zhang et al. [5] also reported that DCAF2 expression in colonic biopsies of IBD inversely correlated with inflammation. These findings were similar to those reported by Huang et al. [3]. In contrast, Fan et al. [4] reported increased DCAF2 mRNA levels in peripheral blood mononuclear cells (PBMCs) obtained from IBD patients, showing a positive correlation of DCAF2 with inflammation. Thus, in IBD patients, elevated DCAF2 in PBMCs [4] and low levels in colonic biopsies were correlated with attenuated inflammation [3, 5].

DCAF2 may hold promise as a druggable target once its function in different tissues is further clarified. Since global knockout of DCAF2 in mice is not possible due to viability issues [7], more information is needed about its function in different immune cells implicated in IBD. For instance, in the current study, colonic biopsies were used to measure the DCAF2 levels. Nevertheless, simultaneous measurement of DCAF2 levels were obtained in PBMCs with corresponding cytokine levels would have improved the understanding of DCAF2 function in autoimmunity. Besides, exploring possible epigenetic modifications in the gene sequences of DCAF2 in IBD patients could further the understanding of other functions of this protein, such as posttranslational modification of ubiquitination pathways.

Thus, the current study, along with previous reports on DCAF2 when expressed in T cells, and DCs in different autoimmune diseases paves the way to further the understanding of this intriguing protein.

Declarations

Conflict of interest The author discloses no conflict of interest.

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