

Selective IgA₂ deficiency in a patient with small intestinal Crohn's disease

To the Editor: The human IgA response is composed of two antibody subclasses, IgA₁ and IgA₂. With a shorter hinge region, IgA₂ is more resistant to bacterial proteases. Anecdotal evidence of IgA₂ deficiency is available (1–3); however, no associations with clinical manifestations have been reported. Here, we describe a patient with selective IgA₂ deficiency (CD068) with concomitant small intestinal Crohn's disease (CD) and duodenal and ileal inflammation. To our knowledge, this is the first case of IgA₂ deficiency with a potential link to inflammatory bowel disease (IBD). This report might provide insights into potential IgA₂-specific functions.

Ileal cells, colonic cells, and PBMCs were profiled from patient CD068, 19 healthy donors (HDs), and 15 patients with IBD (Supplemental Table 1; supplemental material available online with this article; <https://doi.org/10.1172/JCI167742DS1>). Total absence of IgA₂⁺ plasma cells (PCs) (Figure 1A) and switched memory B (B_{mem}) cells (Figure 1B) was noted in CD068 but not in HDs. The frequency of ileal and colonic IgA₁⁺ PCs and B_{mem} cells was comparable in CD068, patients with IBD, and HDs (Figure 1C and Supplemental Figure 1B). Conversely, a significant loss of IgA₂⁺ PCs was detected in inflamed colonic areas from patients with UC compared with HDs, while a trend toward loss of IgA₂⁺ cells in inflamed ileal tissues from patients with CD was noted (Figure 1C). We also found a significant expansion of IgG⁺ PCs in inflamed ilea and colons of patients with IBD compared with HDs. An increase in IgG⁺ PCs (above HD interval estimate) was observed in both inflamed (ileum) and uninfamed (colon) tissues of CD068 (Figure 1C). In a subset of individuals, paired colon/ileum samples were analyzed in parallel (Supplemental Figure 1C). Using tissue immunofluorescence, we found no IgA₂⁺ cells in the intestinal mucosa of CD068, while IgA₁⁺ cells were readily detected (Figure 1D). To exclude a lack of detection by our primary antibody, we stained tissue for IgA₁ and total IgA and obtained comparable results (Supplemental Figure 1E).

In contrast to that in HDs, we could not detect IgA₂ in the serum or ileal biopsy culture supernatants in CD068, (Figure 1E). Levels of IgA₂ in circulation were comparable between HDs and patients with CD (Figure 1F). The concentration of all antibody isotypes except IgA₂ was comparable between CD068 and HDs (Figure 1G). PBMCs stimulated with CD40L and IL-21 induced both IgA₁⁺ and IgA₂⁺ PCs in HDs, but no IgA₂⁺ PCs were induced in CD068 (Supplemental Figure 1F). In an effort to identify a genetic basis for IgA₂ deficiency, we used a 407-gene panel for immune deficiency, but no homozygous alterations were detected (Supplemental Table 2).

Next, we examined IgA-coated stool bacteria (Figure 1H) and found a complete lack of IgA₂ coating. Metagenomic sequencing of stool samples in 10 HDs, 7 patients with CD, and CD068 revealed a loss of α diversity in patients with CD and CD068 compared with HDs (see Supplemental Methods). Furthermore, gut bacteria from CD068 and CD samples clustered together (Figure 1I and Supplemental Figure 1G). Finally, a distinct expansion of Clostridiales and a loss of Bacteroidales was observed in CD068. To evaluate

potential consequences of intestinal dysbiosis, we measured circulating zonulin as well as IgG and IgA against *Saccharomyces cerevisiae* (ASCA) at two different time points (Figure 1J). Zonulin levels were similar in HDs and patients with CD (both $n = 10$) but were elevated in CD068. In addition, ASCA IgA and IgG concentrations from CD068 were among the highest in a large database of HDs and patients with CD ($n = 367$, $n = 806$). These data demonstrate that, in CD068, lack of IgA₂ was associated with gut dysbiosis, impaired gut barrier integrity, and exaggerated systemic antibody responses to commensals.

Given its higher resistance to proteolysis, IgA₂ may be particularly involved in immune exclusion, and its lack could increase epithelial penetration by commensals. Accordingly, major B cell perturbations in inflamed IBD tissue have been described previously (4), including a loss of IgA₂⁺ PCs (5). The small intestine is the largest reservoir of IgA⁺ PCs in the body and includes bacterial communities more heavily coated by IgA than those from the colon (6), which could render the small intestine more susceptible to tissue injury due to impaired IgA (or IgA₂) production. Although a causal relationship between the lack of IgA₂ and CD remains unproven, we believe our study shows novel evidence that documents an association between IgA₂ deficiency and small bowel CD with duodenal inflammation. Further studies aimed at dissecting the specific function and reactivity of gut IgA₁ and IgA₂ could lead to a better understanding of the contribution of IgA subclasses to IBD pathogenesis.

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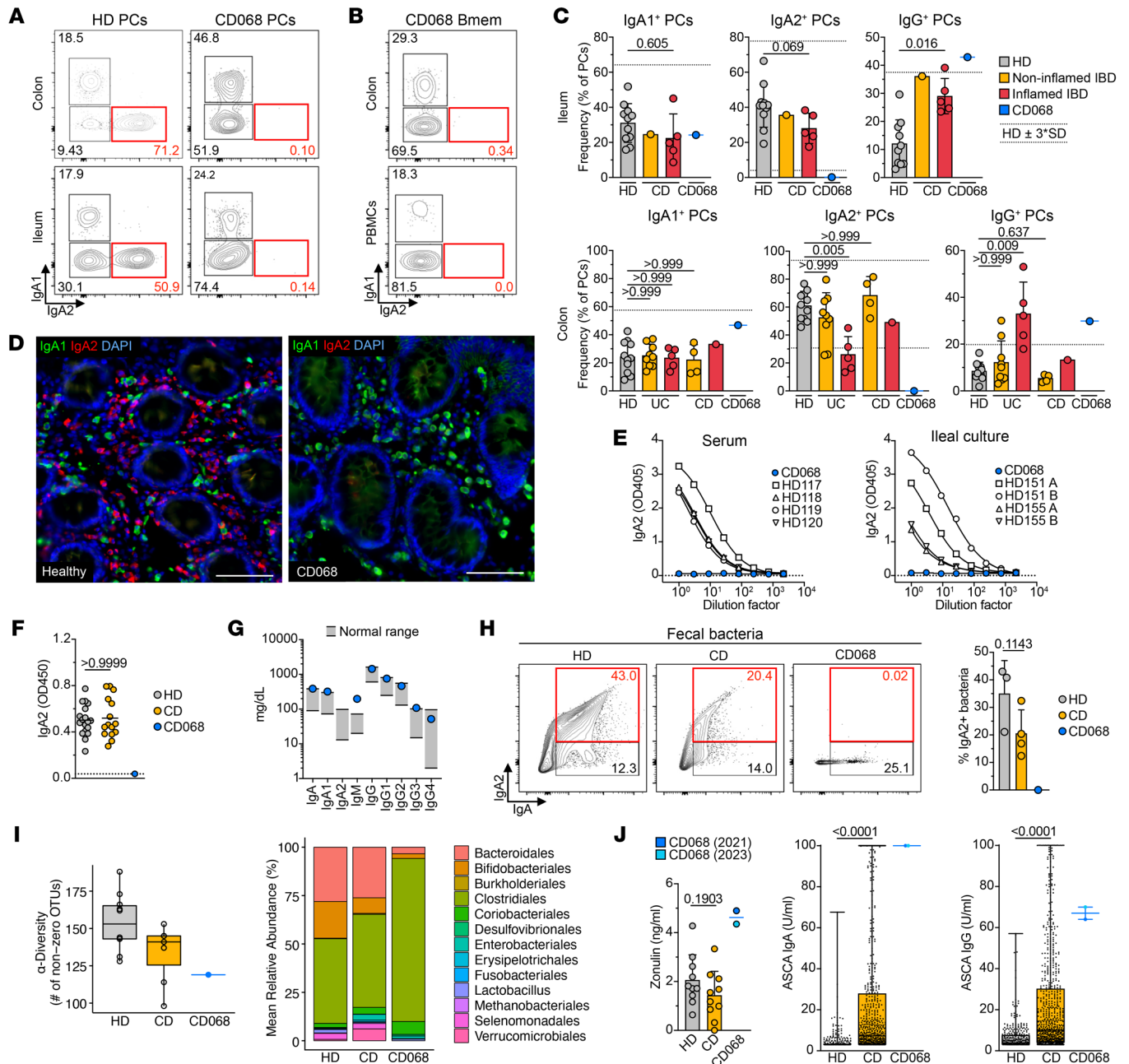


Figure 1. Selective IgA₂ deficiency in a patient with small intestinal CD. Flow cytometry staining of IgA₁ and IgA₂ on (A) intestinal PCs from a representative HD and patient CD068 and (B) memory B (B_{mem}) cells in colon and circulation from CD068. (C) Frequency of intestinal PCs from HDs ($n = 19$), patients with IBD ($n = 15$), and CD068. Each point represents a sample. Mean \pm SD, and interval estimate are shown. (D) Immunofluorescence staining of IgA₁ and IgA₂ from a representative HD and CD068. Scale bar: 80 μ m. (E) Secreted IgA₂ levels in the serum and ileal tissue culture supernatant of HDs and CD068. (F) Plasma IgA₂ in HDs ($n = 18$), patients with CD ($n = 15$), and CD068. (G) Total serum immunoglobulins from HDs (gray) and CD068. (H) Representative flow cytometry plots and quantification of IgA⁺ and IgA₂⁺ microbiota in HDs ($n = 3$), patients with CD ($n = 4$), and CD068. (I) Metagenomic sequencing analysis from fecal samples, including α diversity and relative abundance (HD, $n = 10$; CD, $n = 7$). (J) Circulating zonulin and ASCA IgG and IgA in HDs ($n = 367$), patients with CD ($n = 806$), and CD068. All comparisons were done with Mann-Whitney test, except in C, where Kruskal-Wallis test and Dunn's test was used. P values are shown.

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Conflict of interest: See supplemental conflict-of-interest statement.

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