

Letters to the Editor

Constitutive gut-homing capacity on circulating myeloid dendritic cells in coeliac disease

Key words: Dendritic cells. Coeliac disease. Homing. Migration. Blood.

Dear Editor,

Coeliac disease (CD) is a small intestine immune enteropathy to gluten-containing cereals developed in genetically (HLA-DQ2⁺) predisposed individuals resulting in a pro-inflammatory T-cell mediated duodenal response characterized by villous atrophy, crypt hyperplasia and increase infiltration of intraepithelial lymphocytes. Its only treatment is a permanent strict gluten-free diet (GFD) after which the immune response is abrogated leading to clinical remission of the disease (1).

Dendritic cells (DC), the most potent antigen presenting cells, control the type and location of immune responses by differentiating antigen-specific effector T-cells (2) and directing them to the target tissue via homing marker imprinting (3,4). DC are therefore central in CD pathogenesis as they present gluten antigen to T-cells in a HLA-DQ2 restricted manner generating gluten-specific pro-inflammatory gut-homing T-cells (5). DC themselves also express homing markers displaying a multi-homing potential in the blood from healthy controls (HC) (6). However, the homing marker profile of blood DC is altered during gut inflammation. Circulating DC from patients with Crohn's disease restricted to different anatomical locations (e.g. large vs. small bowel) display altered homing markers expression which may correlate with DC infiltrates

at those sites (7). Indeed, patients with small bowel Crohn's disease had decreased expression of the skin homing molecule CLA rendering circulating DC with an increased $\beta 7^+ \text{CLA}^-$ gut homing phenotype (7). Such findings suggest that assessing blood DC homing profile may be a useful diagnostic tool to assess the phenotype/status of such patients. However, as DC do not recirculate it is difficult to understand how they display altered homing profile trafficking them to the target tissue where the inflammation is ongoing. Indeed, such altered DC homing profile could be a constitutive factor of the disease or on the contrary be consequence of the ongoing gastrointestinal inflammation which has the capacity to modulate –via secreted cytokines– homing profile and homing-imprinting capacity of DC (8). To further our understanding in the mechanisms of the altered DC trafficking in gastrointestinal disease, here we assessed the homing profile of another small bowel condition, CD, focusing on GFD-treated patients.

Circulating DC were identified by flow cytometry as HLA-DR⁺CD3⁻CD14⁻CD16⁻CD19⁻CD34⁻. Myeloid (mDC) and putative plasmacytoid DC (pDC) were further identified as CD11c⁺ and CD11c⁻ respectively (Fig. 1A). There was no difference in the percentage or type of circulating DC between HC (with not known autoimmune diseases or malignancies) and CD-GFD patients. In agreement with our previous findings circulating mDC from HC displayed a multi-homing $\beta 7^+ \text{CLA}^+$ phenotype (6). On the contrary, mDC from GFD-CD patients had decreased CLA expression (Fig. 1 B and C) rendering mDC with an increased gut homing $\beta 7^+ \text{CLA}^-$ profile (Fig. 1C) as in small bowel Crohn's disease (7). However, in contrast to Crohn's disease patients, GFD-CD patients did not have an ongoing inflammation. All GFD-CD had negative serology and no clinical symptoms of disease. In addition, expression of innate immunity receptors TLR2/4 (Fig. 1D) and activation markers CD40/80 (Fig. 1E) on GFD-CD patients were not differentially expressed from those found in HC confirming the absence of an ongoing inflammation. Finally, altered homing profile remained restricted to the mDC population as no difference was found in the phenotype of circulating CD11c⁻ DC from HC and GFD-CD (data not shown).

Our results suggest that circulating mDC from CD patients have an increased gut-homing profile which does not seem to

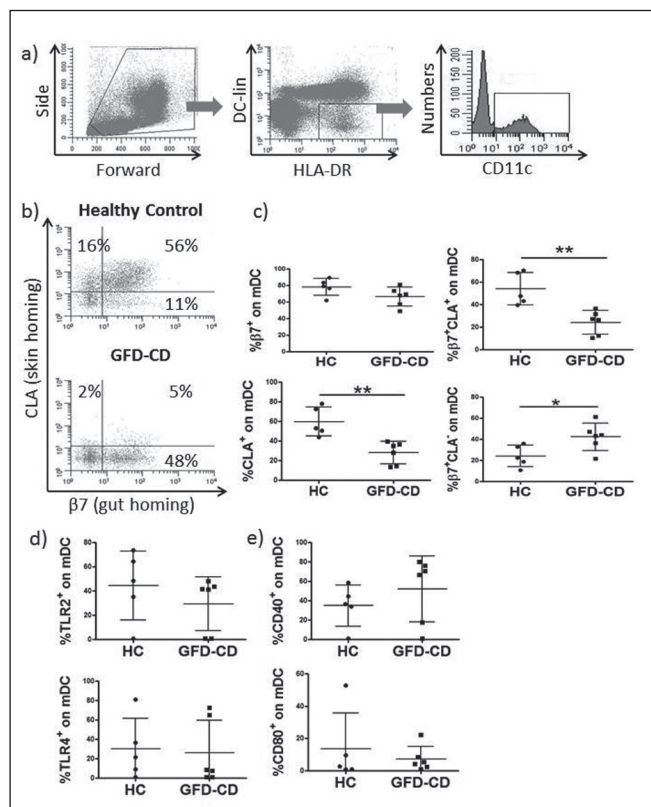


Fig. 1. Increased gut-homing profile on blood mDC from GFD patients. a) Dendritic cells (DC) were identified by flow cytometry within the forward and side scatter live cell as HLA-DR⁺ and negative for markers of other cell lineages (CD3, CD14, CD16, CD19, CD34). Myeloid DC (mDC) were subsequently identified as CD11c⁺. b) $\beta 7$ and CLA homing molecules were studied on blood mDC from healthy controls (HC) and coeliac patients on the gluten-free diet (GFD-CD). Pooled data is shown in c). d) TLR2/TLR4 and e) CD40/80 expression was also studied on blood mDC from HC and GFD-CD patients. Paired t-test was applied, and p-value < 0.05 was considered as statistically significant (*p < 0.05, **p < 0.01).

be a consequence of an inflammatory response of the disease but may be a constitutive characteristic of such patients. Such increased DC gut-homing capacity may have a role in the abnor-

mal response to gluten antigens in CD and could also be used as a diagnostic tool to help in CD diagnosis.

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