Immunological Disorders and Immunotherapy

Li, et al., Immunol Disord Immunother 2016, 1:2

Letter to Editor open access

Accumulation of ILC1 Cells in a DiGeorge Syndrome Patient with Intestinal Inflammation

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Rec date: July 08, 2016, **Acc date:** July 25, 2016, **Pub date:** July 28, 2016

Letter to Editor

DiGeorge Syndrome (DGS) is a genetic disorder caused by a microdeletion of chromosome 22q11.2. Its classical features include congenital heart disease, abnormal facies, speech delay and hypocalcaemia [1]. The gastrointestinal complaints are also very common. However, the mechanisms of DGS with intestinal inflammation remain elusive.

Innate lymphoid cells (ILC) are novel effector lymphocytes which have been shown to play an essential role in the maintenance of intestinal homeostasis. Our previous study has shown that ILC phenotype changed dramatically in the inflamed gut of Crohn's disease (CD) patients compared to unaffected tissue [2]. The frequency of pathogenic IFN-r-producing ILC1 cells increased in the lamina propria at the cost of protective ILC3.

This conversion contributed to the pathogenesis of CD. Here we identified the intestinal ILC phenotype of a DGS patient with intestinal complaints from his ileum biopsy samples and observed similar accumulation of ILC1 cells in his inflamed terminal ileum.

This 28-year-old male presented to our institution with small bowel obstruction. His past medical history was significant for DGS causing chronic constipation since birth. 3 years ago, he underwent total colectomy and had been doing well. Until recently, he had acute onset of abdominal distention, nausea, and vomiting. CT imaging showed small bowel obstruction proximal to ileorectal anastomosis without mechanical obstruction.

Inflammatory markers were elevated (high sensitivity C-reactive protein, 88.1 mg/dl; erythrocyte sedimentation rate, 19 mm/h). Stool culture, *C. difficile* PCR, and Cytomegalovirus blood PCR were negative. Immunological work-up showed severe CD4 lymphopenia (CD4 count 219 cells/μL).

Flexible sigmoidoscopy revealed diffuse exudates in the terminal ileum. HE staining of the biopsy sample showed patchy active ileitis with erosion which was associated with accumulation of mononuclear inflammatory cells. This patient was started on stress dose steroids and TNF-α inhibitor with improvements in his initial symptoms.

Flow cytometry analysis of the biopsy samples from his inflamed ileum demonstrated that the frequency of Lineage-CRTH2-CD45+NKp44-CD117-CD127+ ILC1 cells increased at the loss of NKp44+ILC3. This phenotype was similar to what we observed in the inflamed terminal ileum of CD patients compared to unaffected ileum (Figure 1).

Figure 1A showed differential histological appearances in the terminal ileum of our CD patients and this DGS patient. Compared to unaffected ileum, the frequency of protective NKp44+ILC3 within Lineage-CRTH2-CD45+CD127+ decreased from 63.3% to 40.5% and 23.9% respectively in the inflamed terminal ileums (Figure 1B). At the same time, the percentage of IFN-γ-producing ILC1 increased from 23.3% to 47.3% and 43.6% (Figures 1B and 1C).

Innate lymphoid cells (ILCs) are new players in the innate immunity that can quickly react to the danger signals from the environment. They are deployed as sentinels and serve as the first line of defense along our mucosal barrier surfaces, such as skin, lung and intestine.

According to their specific transcription factors and cytokine production pattern, ILCs are categorized into three groups: ILC1, ILC2 and ILC3 [3].

Under the steady state, NKp44+ILC3s are the dominant non-cytotoxic ILC subset in the human intestine which play a protective role in the maintenance of mucosa integrity and barrier function. The IL-22 secreted by ILC3 can promote the epithelial cells to produce antimicrobial peptides (AMP) to fight with invading pathogens. Also, IL-22 can induce the proliferation of intestinal epithelial cells to contribute to tissue repair process.

Additionally, human intestinal ILC3 can control auto reactive CD4+T cell activation in the lamina propria through its MHCII surface expression. MHCII+ILC3s are able to process and present antigens to CD4+T cells, but different from typical macrophages or dendritic cells, this presentation causes activated commensal bacteria-specific CD4+T cell apoptosis instead of proliferation [4].

However, in the inflamed gut of CD patients, the IL-22-producing NKp44+ILC3s were converted into IFN-γ-producing ILC1 cells which were related to the disruption of the intestinal barrier function [5].

In the inflamed terminal ileum of this DGS patient, there was a similar ILC3/ILC1 conversion and likely initiated the dysregulated intestinal immune responses. It is very rare that DGS is associated with possible auto-inflammatory related intestinal inflammation. It would be interesting to see if there are common defective cellular or molecular mechanisms between DGS patients with intestinal inflammation and CD patients.

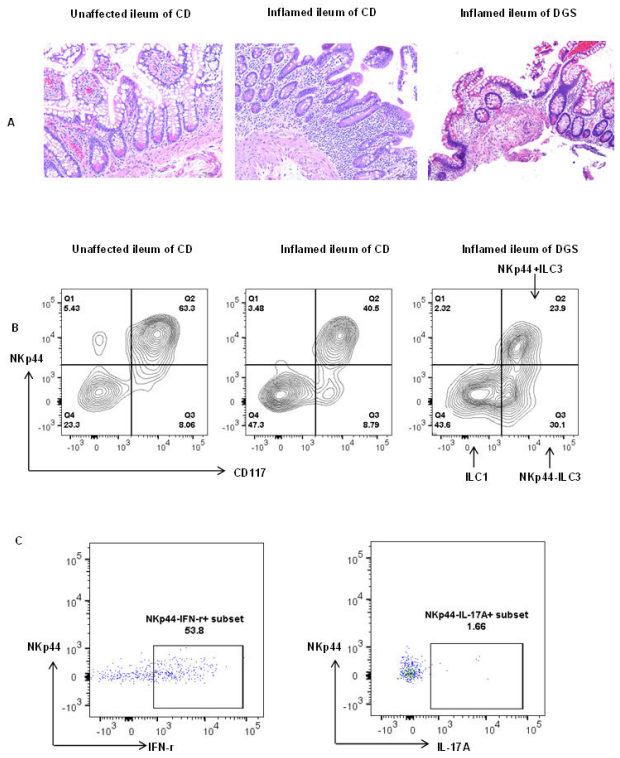

Figure 1: A) Representative HE staining demonstrates distinct histological appearance in the terminal ileum of CD patients and this DGS patient. The left one is the control ileum from one CD patient with no histological alteration. The middle one is an inflamed terminal ileum of a CD patient which showed increased infiltration of immune cells in the lamina propria. The right one is this DGS patient with intestinal inflammation in the terminal ileum which showed the distortation of mucosal archerture and densed infiltration of inflammatory cells in the gut. Scale bars: 100μm. B) The accumulation of Lineage-CRTH2-CD45+NKp44-CD117-CD127+ ILC1 cells in the inflamed terminal ileum of both CD patient and this DGS patient with intestinal inflammation after gating Lineage- CD45+ CRTH2- CD127+LPMC compared to the control ileum. At the same time, the frequency of NKp44+ILC3 decreased in the inflamed terminal ileum of both CD patient and the DGS patient compared to unaffected tissue. The gating strategy is shown in supplemental data. C) Fluorescence-activated cell sorting (FACS)-sorted intestinal ILC1 cells from the inflamed gut of CD patients were potent IFN-γ producers, not IL-17A which might contribute to the process of intestinal tissue damage.

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