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Introduction Crohn's disease (CD) is driven by inappropriate inflammatory responses to gut microbiota. Circulating, microbe-responsive V γ 9V δ 2⁺(δ 2)T cells express 'gut-homing' integrin β 7 and may contribute to intestinal inflammation.

Hypothesis Increased intestinal permeability and microbe exposure in CD leads to activation and expansion of δ 2T cells.

Aim To compare δ 2T cells in CD patients, unaffected siblings and healthy controls (HC).

Methods Flow cytometry was used to gate T cell subsets in 36 CD patients, 13 siblings and 13 HC. δ 2T cell activation and cytokine production in culture of HC and CD peripheral blood mononuclear cells (PBMCs) was assayed upon stimulation with synthetic microbial phosphoantigen (HDMAPP) in vitro.

Results When HC and CD PBMCs were activated by HDMAPP, δ 2T cells proliferated, produced high levels of IFN γ and TNF α , and maintained high integrin β 7 levels in vitro. In CD patients, the variation in numbers of circulating δ 2T cells was significantly ($p=0.02$) greater than in HC (0.1–138.4 vs 6.2–37.8 cells per μ l blood; 0.1–13.0% vs 0.5–2.9% of total T cells). Of the 19 CD patients not treated with thiopurines (TP), 9 had expanded δ 2T cells (number or proportion above upper limit of HC) and of these, 8 (89%) had inactive disease (HBI <5 , $p<0.05$). There was no difference in age, age at diagnosis, CRP, disease location, behaviour or duration between expanded and non-expanded non-TP treated patients. Strikingly, four of 13 siblings also had expanded δ 2T cells (up to 6–10-fold higher than HC values). In long-term TP-treated CD ($n=17$), mean δ 2T cell numbers were significantly lower than both HC ($3.5 \mu\text{l}^{-1}$ vs $19.7 \mu\text{l}^{-1}$, $p<0.001$; 0.5% vs 1.3%, $p<0.01$), and TP-naïve patients ($20.6 \mu\text{l}^{-1}$ $p=0.02$; 2.61%, $p=0.01$) and this effect was selective for δ 2 over $\alpha\beta$ T cells (mean absolute counts 17.4% vs 34.3% of the mean in HC, $p=0.02$). This effect was not evident in 12 patients with TP therapy of <3 months. In vitro, therapeutic azathioprine (AZA) levels ($5 \mu\text{M}$) equally blocked proliferation of $\alpha\beta$ and δ 2T cells, although effects on δ 2T cells were achieved at lower (AZA) than for $\alpha\beta$ T cells ($0.005 \mu\text{M}$ vs $0.05 \mu\text{M}$).

Conclusion Circulating δ 2T cells are disturbed in CD due both to expansion in some individuals as well as depletion in TP-treated patients. Selective depletion of δ 2T cells was not observed during TP induction despite enhanced AZA-sensitivity of stimulated δ 2T cells in vitro. We speculate that repeated microbial stimulation under the cover of immunosuppressants may be required to selectively deplete δ 2T cells. δ 2T cell expansion in patients and siblings may imply a role for δ 2T cells in CD pathogenesis and could be a marker of CD risk.

Competing interests None.

Keywords at-risk phenotype, Crohn's disease, Inflammatory Bowel Disease, Sibling, Thiopurine, δ 2T cell.

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V δ 2+T CELL EXPANSION IN CROHN'S DISEASE: IMPACT OF INFLAMMATION, DISEASE ACTIVITY AND TREATMENT

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