Institute of Cell and Molecular Science, Queen Mary University of London, London, UK; [3]Barts and the London NHS Trust, London, UK

Introduction Crohn's disease (CD) is driven by inappropriate inflammatory responses to gut microbiota. Circulating, microbe-responsive Vγ9Vδ2$^+$(δ2)T cells express 'gut-homing' integrin β7 and may contribute to intestinal inflammation.
Hypothesis Increased intestinal permeability and microbe exposure in CD leads to activation and expansion of δ2T cells.
Aim To compare δ2T 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. δ2T 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, δ2T cells proliferated, produced high levels of IFNγ and TNFα, and maintained high integrin β7 levels in vitro. In CD patients, the variation in numbers of circulating δ2T cells was significantly (p=0.02) greater than in HC (0.1–138.4 vs 6.2–37.8 cells per μl 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 δ2T 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 δ2T cells (up to 6–10-fold higher than HC values). In long-term TP-treated CD (n=17), mean δ2T cell numbers were significantly lower than both HC (3.5 μl^{-1} vs 19.7 μl^{-1}, p<0.001; 0.5% vs 1.3%, p<0.01), and TP-naive patients (20.6 μl^{-1} p=0.02; 2.61%, p=0.01) and this effect was selective for δ2 over αβT 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 μM) equally blocked proliferation of αβ and δ2T cells, although effects on δ2T cells were achieved at lower (AZA) than for αβT cells (0.005 μM vs 0.05 μM).
Conclusion Circulating δ2T cells are disturbed in CD due both to expansion in some individuals as well as depletion in TP-treated patients. Selective depletion of δ2T cells was not observed during TP induction despite enhanced AZA-sensitivity of stimulated δ2T cells in vitro. We speculate that repeated microbial stimulation under the cover of immunosuppressants may be required to selectively deplete δ2T cells. δ2T cell expansion in patients and siblings may imply a role for δ2T 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, δ2T cell.

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

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C R Hedin,[1,2,*] N E McCarthy,[2] S Bhattacharjee,[2] G James,[2] K Whelan,[1] J O Lindsay,[2,3] A J Stagg[2] *[1]Nutritional Sciences Division, King's College London, London, UK; [2]Blizard*