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AUTOPHAGY GENE POLYMORPHISMS INFLUENCE THE INTERACTION OF *E COLI* AND MACROPHAGES IN CROHN'S DISEASE

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T Elliott,^{1,2*} N Prescott,³ B Hudspeth,² N Rayment,² J Hermon-Taylor,² J Brostoff,² C Mathew,³ J D Sanderson^{1,2} ¹Department of Gastroenterology, Guys and St Thomas' Hospital, London, UK; ²Nutritional Sciences Division, King's College London, London, UK; ³Department of Medical and Molecular Genetics, King's College London, London, UK

Introduction A well established expression of the proposed defect in innate immunity in Crohn's disease (CD) is the prolonged survival of strains of *Escherichia coli* in peripheral blood monocytes/macrophages (PBM) from patients with CD compared to those from healthy controls (HC). Altered handling of *E coli* in CD has been demonstrated in PBM and in-situ in CD by laser dissection of *E coli* infected macrophages. Several of the gene polymorphisms conferring an increased risk of CD occur in genes involved in bacteria-immune cell interactions. The aim of this study was to determine the influence of these polymorphisms on the interaction of *E coli* with CD-derived monocyte / macrophages.

Methods PBM's and lamina propria macrophages were obtained from 43 and 17 CD patients respectively (mean age 39 years / range 20–70 years). PBM's were challenged with *E coli* and then the response of these PBM's measured by levels of bacterial killing, using the gentamicin protection assay. Phagocytosis and reactive oxygen radicals (ROR's) production were measured by flow cytometry using the phagotest and phagoburst assays. Cytokine (TNF α , IL10, IL23) production was measured by ELISA. In parallel experiments, TNF α , IL10 and CD163 expression was measured by qRT-PCR in laser dissected *E coli* laden and unladen lamina propria macrophages. All patients were genotyped for the three common NOD-2 SNP's (G908R, L1007fs and R702W), and the autophagy related SNP's (ATG16L1 and IRGM). Genotypes and monocyte/macrophage markers were compared.

Results Presence of the ATG16L1 risk variant was strongly associated with a reduced *E coli* induced TNF α expression in CD PBM's ($p=0.0017$) and increased levels of ROR's on uptake of CD derived *E coli* ($p=0.0027$). Presences of IRGM risk variant was associated with increased IL10 expression from PBM's. NOD-2 mutations were not associated with a difference in any variable studied. No genotype altered survival of *E coli* in PBM at 2 or 4 h after infection or *in-situ* lamina propria macrophage cytokine expression.

Conclusion These results show that defective autophagy modifies the handling of intracellular bacteria in CD but appears unlikely to be the main cause of prolonged bacterial survival. Further studies are needed to elucidate the nature of this innate defect and its role in CD pathogenesis.

Competing interests None.