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DEFECTIVE MACROPHAGE FUNCTION IN CROHN'S DISEASE: ROLE OF ALTERNATIVELY ACTIVATED MACROPHAGES IN INFLAMMATION

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Introduction The aetiology of Crohn's disease (CD) involves a genetically determined dysregulated immune response to commensal intestinal microflora. In CD, viable *E coli* are found within lamina propria macrophages (MΦs) and *E coli* intracellular survival is prolonged in CD-derived MΦs in vitro. Different MΦ subpopulations exist, M1 cells are inflammatory cells, M2a cells are involved in tissue repair and M2c are regulatory cells that limit inflammation. The role these different MΦs play in this abnormal handling of bacteria in CD is unclear.
Methods The aim of this study was to examine in vitro M1 and M2 MΦ maturation in CD patients and healthy individuals and how these cells respond to challenge with CD-derived *E coli*. To do this we monitored MΦ morphology, surface markers and cytokine production and intracellular bacterial survival. Peripheral blood monocytes were isolated from CD

patients and healthy controls and treated with cytokines to generate distinct MΦ subpopulations: IFNγ for M1, IL4/IL13 for M2a and IL10 for M2c. MΦ morphology was assessed by H&E staining and surface marker expression of CD14, CD16 and CD33, chemokine receptor CCR2, scavenger receptor CD163, co stimulatory molecule CD40 and mannose receptor CD206 using flow cytometry. IL10 and TNFα production were measured by ELISA and intracellular *E coli* survival was measured using the gentamicin protection assay.

Results In contrast to M1 MΦ's, both CD-derived M2 populations failed to develop the characteristic MΦ dendrite morphology seen in control macrophages. Surface expression of CD40 in M2 CD-derived MΦs was 3.4-fold lower for M2a and 4.4-fold lower for M2c compared to controls after *E coli* challenge. CD163 was higher in M1 CD cells but reduced by 50% in M2 cells compared to healthy cells. After *E coli* challenge, TNFα production by M2 but not M1 MΦs was significantly lower in CD than in controls (M2a 38%, M2c 27% respectively less than controls) but there were no differences in IL10 production. Prolonged intracellular survival of *E coli* was demonstrated in CD M2 cells but effective killing occurred in all M1 CD MΦs and all control MΦs.

Conclusion In CD, M2 (but not M1) MΦs display abnormal morphological maturation, lower TNFα levels after *E coli* challenge, prolonged intracellular bacterial survival and differences in surface marker expression. The results are consistent with an innate MΦ defect in CD relating particularly to a failure of the normal role of M2 MΦs to limit and control inflammation.

Competing interests None.

Keywords Macrophage.