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$IgD^{-}CD27^{-}$ double negative B cells in multiple sclerosis patients are mature memory cells that can migrate towards pro-inflammatory chemokines

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Background and Aims

Pro-inflammatory age-associated $IgD^{-}CD27^{-}$ double negative (DN) B cells are abnormally elevated in the peripheral blood and cerebrospinal fluid of multiple sclerosis (MS) patients. This study aimed to investigate the developmental and migratory phenotype and function of DN B cells in MS.

Methods

Expression of developmental markers was determined on DN, $IgD^{-}CD27^{+}$ class-switched memory (CSM) and $IgD^{+}CD27^{-}$ naive B cells of healthy controls (HC, n=48) and MS patients (n=96) by flow cytometry. Pro-inflammatory chemokine receptors and the transcription factor T-bet, previously described in another pathological age-associated B cell subset, were measured on B cell subsets of HC (n=25) and MS patients (n=49). Using an in vitro chemotaxis assay, migration of MS (n=7) B cell subsets was studied.

Results

DN B cells are mature antigen-experienced cells as indicated by low CD5, CD10 and CD38 expression and IgG or IgA expression in the majority of cells. However, IgA^{+} and activated $CD95^{+}$ cells were less frequent in DN versus CSM B cells. DN B cells showed the highest T-bet expression and similar expression of chemokine receptors CXCR3 and CXCR5 compared to naive and CSM B cells, respectively. MS DN B cells further showed a high migration capacity towards CXCL10 (CXCR3 ligand) and CXCL13 (CXCR5 ligand) that was similar to CSM B cells.

Conclusions

DN B cells resemble CSM B cells but are at an earlier maturation state. Their potential importance in MS pathology was underlined by their migration towards chemokines important for B cell migration through the blood-brain barrier in MS.