Cerebrospinal fluid levels of “B-Cell Maturation Antigen” (BCMA, TNFRSF17) are increased in MS and correlate with B cells.

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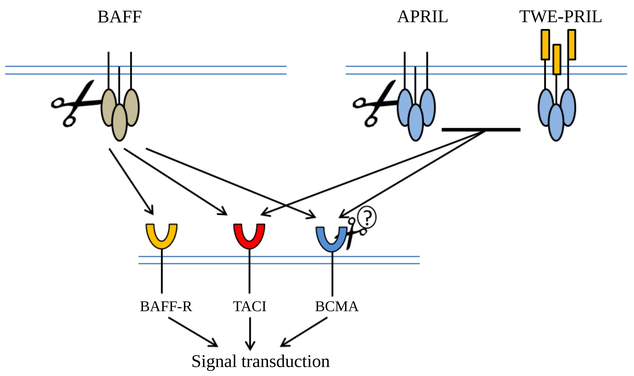
Background

Recent work highlights the contribution of B cells to CNS inflammation and pathogenesis of MS: In the majority of MS patients, B cell numbers are elevated in the CNS, and Rituximab has been shown to reduce the disease activity in multiple sclerosis. Additionally, meningeal B cell follicles were found in close proximity to large subpial gray matter lesions and diffuse meningeal inflammation. This suggests that the lymphoid-like follicles or products produced by them negatively impact the integrity of the cortical structures and contribute to gray matter cortical demyelination (Magliozzi R; Brain. 2007 Apr; 130(Pt 4): 1089-104).

Peripheral B-cell maturation, homeostasis, and antigen-dependent differentiation are complex processes occurring in distinct anatomic locations. Nonetheless, steady progress is being made in understanding the molecular cues that govern B-cell fate at each of these distinct stages of differentiation. **BAFF** (TNFSF13B) is known to play a very important role in B cell development and homeostasis (Mackay F; Nat Rev Immunol. 2009 Jul; 9(7):491-502. Review). Three receptors for BAFF have been identified – **BCMA** (TNFRSF17), **TACI** (TNFRSF13B) and **BAFF-R** (TNFRSF13C). All of them are expressed by B lymphocytes. TNFRSF17 and TACI also bind APRIL and an APRIL-TWEAK hybrid called TWE-PRIL, whereas the BAFF-receptor exclusively interacts with BAFF.

BCMA family



Overview of the BCMA superfamily of TNF superfamily ligands and receptors (adapted from Mackay *et al.* (Nature Rev. of Immunol 2009))

Methods

We studied the expression of BCMA by cells derived from the cerebrospinal fluid (CSF) of untreated MS- and control patients by microarray hybridization. In addition, we quantified soluble BCMA and CXL13 protein as well as B-cell number in CSF samples by ELISA and flow cytometry, respectively.

Objective

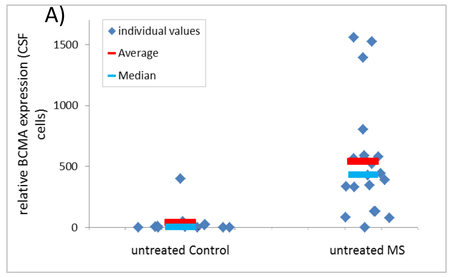
B cells play an essential role in the humoral immune response in neuroinflammation and serve as antigen presenting cells for T cells. The B-cell maturation antigen is a member of the superfamily of TNF receptors and preferentially expressed in B-cells. By interacting with the TNF family members APRIL (TNFSF13) and BAFF (TNFSF13B), BCMA is supposed to play an important role in B-cell homeostasis.

We are aiming to determine if multiple sclerosis (MS) modulates BCMA expression within the CNS.

Summary

- BCMA expression by CSF cells higher in MS patients vs. control patients and in active MS patients vs. inactive MS patients
- Soluble BCMA protein detectable in human CSF
- MS patients have increased BCMA CSF levels
- BCMA CSF levels correlate with B cell number in CSF and CXCL13 levels
- Rituximab does not lower BCMA CSF levels. Hence, increased BCMA CSF levels in MS are not just a result of B cell infiltration during the course of the disease.

Results

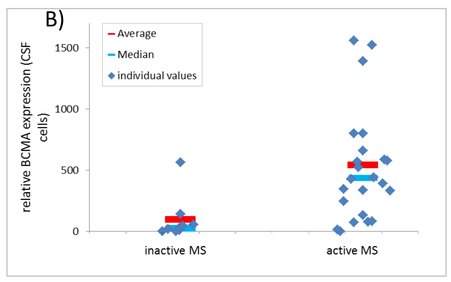


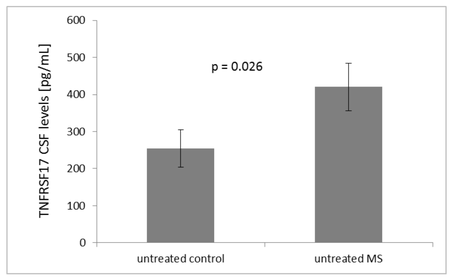
Increased BCMA expression by CSF cells of MS patients

CSF cell transcriptome was analyzed by microarray hybridization (Affymetrix Human Genome U133 plus 2.0; probe set 206641_at).

A: BCMA expression by CSF cells of untreated control patients (n = 9) and untreated MS patients (n = 22); p-value = 6 x 10^{-5}, Student´s T test.

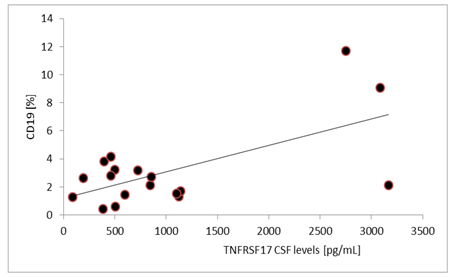
B: BCMA expression by CSF cells of inactive (n = 9) and active MS patients (n = 21), p-value = 2.4 x 10^{-4}, Student´s T test. All patients were untreated for at least a year.





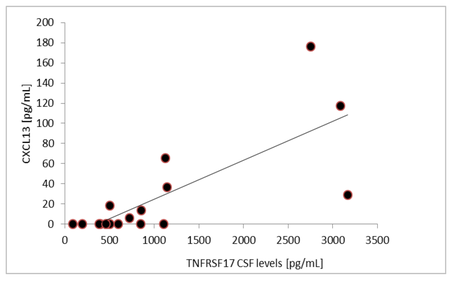
Increased soluble BCMA CSF levels in MS patients

BCMA CSF levels (± s.e.m.) were quantified by ELISA (R&D Systems). BCMA CSF levels of untreated control patients (n = 14) were compared with untreated MS patients (n = 23), p-value = 0.026, Student´s T test).

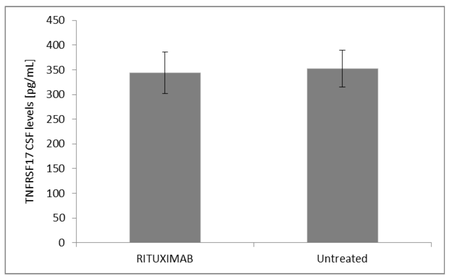


BCMA CSF levels correlate with B cells and CXCL13

BCMA CSF levels correlate with number of CD19+ B cells in CSF of untreated MS patients (Pearson correlation coefficient 0.631, p-value 0.0049).



BCMA CSF levels correlate with CXCL13 CSF concentrations in MS patients (Pearson correlation coefficient 0.765, p-value 0.0002). CXCL13 CSF levels were reported before to correlate with B cell CSF levels (Kowarik, MC; J Neuroinflammation 2012 May 16; 9:93)



soluble BCMA CSF levels are not reduced by Rituximab treatment

BCMA CSF levels (± s.e.m.) of Rituximab-treated MS patients (n = 20) were compared with untreated MS patients (n = 20), p-value = 0.49, Student´s T test). Rituximab reduces number of B cells in the CSF of MS patients (Cross AH; J Neuroimmunol 2006 Nov; 180(1-2):74-78)

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