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Supplementary information

B cells in central nervous system disease: diversity, locations and pathophysiology

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Table 1. Locations of B cells in CNS disorders

Disease	Locations in the CNS								References
	CSF		Meninges		Perivascular		Parenchyma		
	B cells	Plasma cells	B cells	Plasma cells	B cells	Plasma cells	B cells	Plasma cells	
Glioblastoma	?	?	?	?	++/+/-	?	+/-	?	[1]
Meningioma	?	?	++/+/-	+/-	++/+/-	+/-	+/-	+/-	[2]
B cell lymphoma	?	?	+++/-	+++/+/-	+++	+++/+/-	+++/-	+++/+/-	[3,4]
COVID-19	++/+	++/+	?	?	?	?	?	?	[5,6]
CNS tropic viruses	?	++	?	++/+	++/+	++/+	+/-	++/+	[3,7-11]
Bacterial encephalitis	++	++	?	?	?	?	?	?	[8,9,12]
NMO	++/+	++	?	?	++/+	?	?	?	[13,14]
MOG antibody-associated disorder	?	?	?	?	++	?	+	?	[14]
Anti-NDMAR encephalomyelitis	++	++	+++/++	+++/++	+++/++	+++/++	+	++/+	[15,16]

+++ = present in abundance, ++ = present as a minor population, + = non-zero representation, - = not present

? denotes uncertainty about cell numbers in this location.

Table 2. B cell subsets in the CNS of MS or its mouse models

B cell subset	Locations in the CNS				Additional details	References
	CSF	Meninges	Perivascular	Parenchyma		
Naïve B cells - Mouse	B1: +? B2: ++?	B1: + B2: +++	B1: +? B2: ++	B1: -? B2: +	- Many acquire pro-inflammatory characteristics in EAE models.	17-27
Naïve B cells - Human	B1: ++/+ B2: ++/+	B1: ? B2: +	B1: ? B2: +	B1: - B2: -		
Memory B cells - Mouse	IgM: +/-? IgA: +/-? IgG: +/-?	IgM: + IgA: -? IgG: ++/+/-	IgM: +/-? IgA: -? IgG: +/-?	IgM: +/-? IgA: -? IgG: +/-?	- Strongly associated with MS progression. - Most memory cells in CSF are IgM or IgG1.	10,17,19,22-29
Memory B cells - Human	IgM:++/+ IgA:+ IgG:++	IgM:++/+ IgA: + IgG:++	IgM:++/+ IgA: + IgG:++	IgM: +/- IgA: -? IgG: +		
Tbet^{+} memory B cells* - Mice	?	?	-/+/++?	?	-Atypical memory B cells accumulate in the brain with age	27,30
Tbet^{+} memory B cells* - Human	++	++	++/+?	+?	- Predicted presence in the CNS is based on the concentration of atypical memory B cells and CXCR3^{+} B cells within the CNS of MS patients which overlaps with the Tbet^{+} B cell phenotype.	24,31,32
Plasma cells - Mouse	IgM: +? IgA: +? IgG: +?	IgM: + IgA: + IgG: +	IgM: + IgA: + IgG: +	IgM: + IgA: + IgG: +	- Most of the IgG^{+} plasma cells are IgG1 but IgG3 plasma cells likely increase during relapses based on the isotype composition of oligoclonal bands. Small numbers of	8,10,23-25,28,33-38
Plasma cells - Human	IgM: ++/+ IgA: +	IgM: + IgA: +	IgM: + IgA: ++/-	IgM: +/- IgA: +/-		

	IgG: ++	IgG: ++	IgG: ++	IgG: +	IgG2 and IgG4 plasma cells likely exist as well. - IgA1 is the dominant IgA isotype in CSF and lesions although $IgA2^+$ cells can be found. - Expansion of IgM^+ plasma cells is associated with more severe disease. - Most of the plasma cells in CSF have a plasmablast phenotype.	
Regulatory B cells - Mouse	Breg: +? IgA Plasma cell: +?	Breg: ++/+ IgA Plasma cell: +?	Breg: +/-? IgA Plasma cell: ++?	Breg: -? IgA Plasma cell: +?	- IgA^+ regulatory plasma cells are gut-derived and are predominantly found in active white matter MS lesions.	10,21,23,39,40
Regulatory B cells - Human	Breg: ++ IL-10^+ IgA Plasma cell: +?	Breg: ? IL-10^+ IgA Plasma cell: +/-	Breg: ? IL-10^+ IgA Plasma cell: +	Breg: ? IL-10^+ IgA Plasma cell: ++/+		
Germinal center B cells* - Mouse	-?	++/-	-	-	- Predicted presence is based on evidence of somatic hypermutation occurring within the CNS, AID^+ B cells in follicle-like structures and CSF, grouped $Ki67^+$ B cells in follicle-like structures and CSF, and the presence of T follicular helper cells within the CSF and MS lesions. In contrast, the master transcription factor of germinal center B cell differentiation Bcl6, is poorly represented in follicle-like structures.	17,22,25,28,29, 41-47
Germinal center B cells* - Human	+/-	++/-	+/-?	-		

+++ = present in abundance on average, ++ = present as a minor population on average, + = non-zero representation, - = not present
*Evidence is suggestive of the existence of these cells however not definitively proven.
? denotes uncertainty about the precise localization and cell numbers.

Table 3. B cell chemokines and survival factors in the CNS

Chemokine(s)/ survival factor – receptor(s)	Cells affected	Chemokine location	Chemokine expression and disease associations	References
CXCL10 and CXCL9 – CXCR3	Plasmablasts, plasma cells, and Tbet memory B cells.	- Found in perivascular spaces, the meninges, and the parenchyma of MS lesions. - Made by astrocytes.	- CXCL10 is increased in CSF in RRMS and variably in progressive MS.	13,32,47-51
CXCL12 – CXCR4	Germinal center B cells, memory B cells, plasmablasts and plasma cells.	- Found in perivascular spaces - Can be made by astrocytes and by oligodendrocyte precursor cells in EAE.	- Increased in CSF and MS lesions - Correlated with faster cortical thinning and relapses	17,20,37,52,53
CXCL13 – CXCR5	Naïve B cells, germinal center B cells, memory B cells, T follicular helper cells.	- Found in active lesions in the meninges, perivascular spaces, and the parenchyma.	- Increased in MS lesions and CSF throughout the disease - Correlated with disease severity, relapses, new white matter lesions, new cortical lesions, increased immunoglobulin synthesis in CSF, and faster cortical thinning.	12,20,35,43,46,47, 49,52,54,55
CCL19 – CCR7	Naive B cells, activated B cells, memory B cells.	- Found in the meninges and to a lesser degree in perivascular cuffs and may be in the parenchyma. - Expressed by astrocytes and microglia in EAE including within the parenchyma	- Increased in CSF of RRMS and SPMS patients.	20,47,48,56-58
CCL21 – CCR7	Naïve B cells, activated B cells, memory B cells.	- Not found in the parenchyma but small amounts of RNA are found in perivascular cuffs and the meninges. - In perivascular spaces in EAE.	- Present but not increased in CSF in MS.	20,46-48,56-58

CCL20 – CCR6	B1 cells, Naïve B2 cells, Memory B cells	- mRNA detected in perivascular spaces and the meninges.	- Present in small amounts but not increased in CSF in MS.	[20,35,47,59]
CCL2 – CCR2	Naïve and memory B cells.	- mRNA detected in perivascular spaces and the meninges. - Protein detected in the parenchyma - Made by astrocytes in white matter lesions but not grey matter	- Normal to decreased levels in CSF during MS.	[35,47,48,60-62]
CXCL8 – CXCR1 and CXCR2	A small portion of peripheral blood B cells	- Trend towards increased expression in white matter lesions.	- Increased in CSF of MS patients.	[35,52,60,63]
BAFF – BAFF-R and TACI	Naïve B cells, activated B cells, memory B cells, and plasma cells.	- Found in the meninges and to a lesser extent in the perivascular spaces and parenchyma. - Made by astrocytes in lesions	- Slightly increased to decreased in CSF, decreasing during periods of B cell expansion.	[12,37,47,54,64,65]
APRIL – BMCA and TACI	Memory B cells, plasmablasts, and plasma cells.	- mRNA detected in perivascular spaces and to a lesser extent in the meninges. - Made by astrocytes in EAE lesions in the meninges, perivascular spaces, and the parenchyma.	- Slightly increased in MS - Correlated with relapses	[12,37,47,52,64]

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