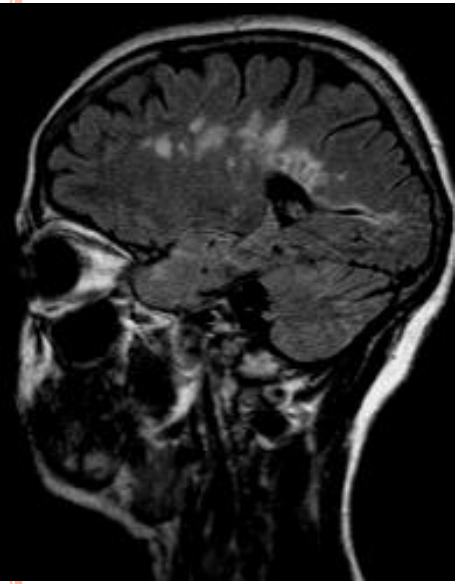
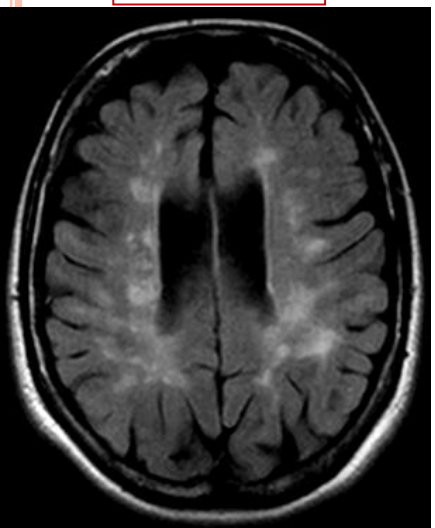
ΝΕΌΤΕΡΑ ΔΕΔΟΜΈΝΑ ΣΤΗΝ ΠΑΘΟΓΕΝΕΣΗ ΤΗΣ ΣΚΛΉΡΥΝΣΗΣ ΚΑΤΆ ΠΛΆΚΑΣ

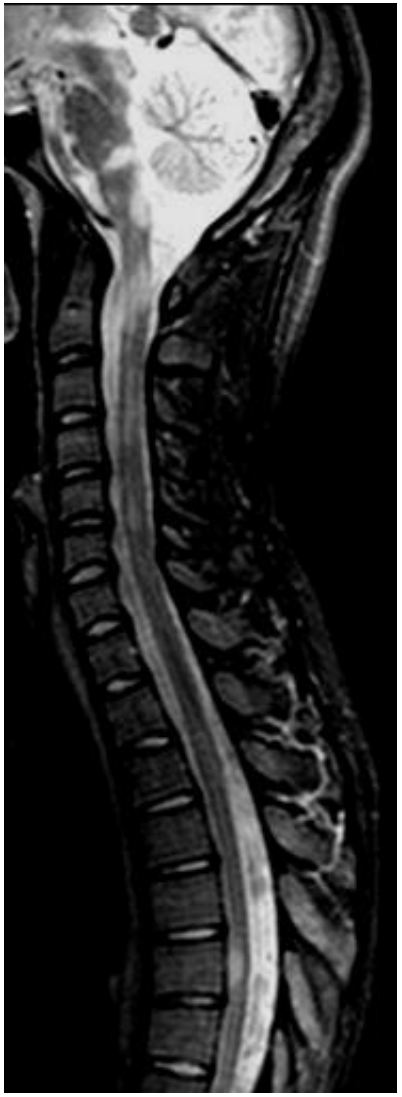
Βασίλειος Χ. Μαστοροδήμος MD, PhD
Διευθυντής ΕΣΥ, Νευρολογική Κλινική ΠΑΓΝΗ

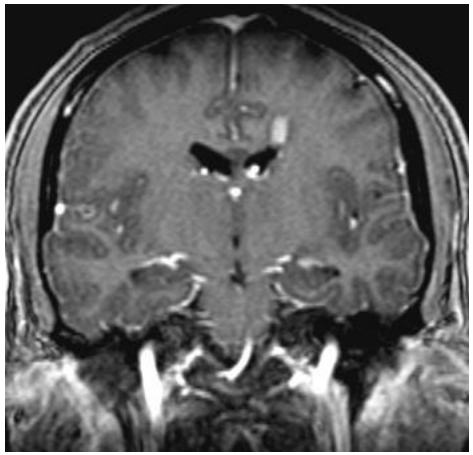
Multiple Sclerosis (MS) is a neurological disease characterized clinically by dissemination in time and space and pathologically by demyelinating plaques



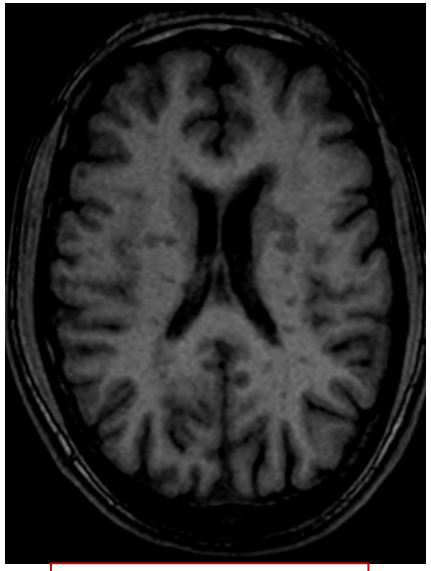
FLAIR



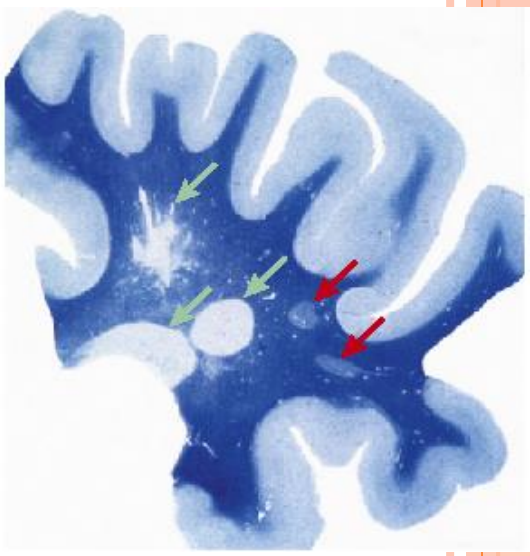




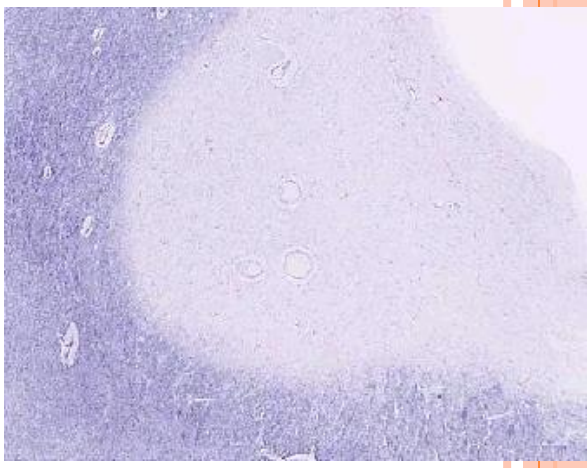
T1Gd+



T1 black holes



Acute demyelinating lesions



Chronic demyelinating plaque

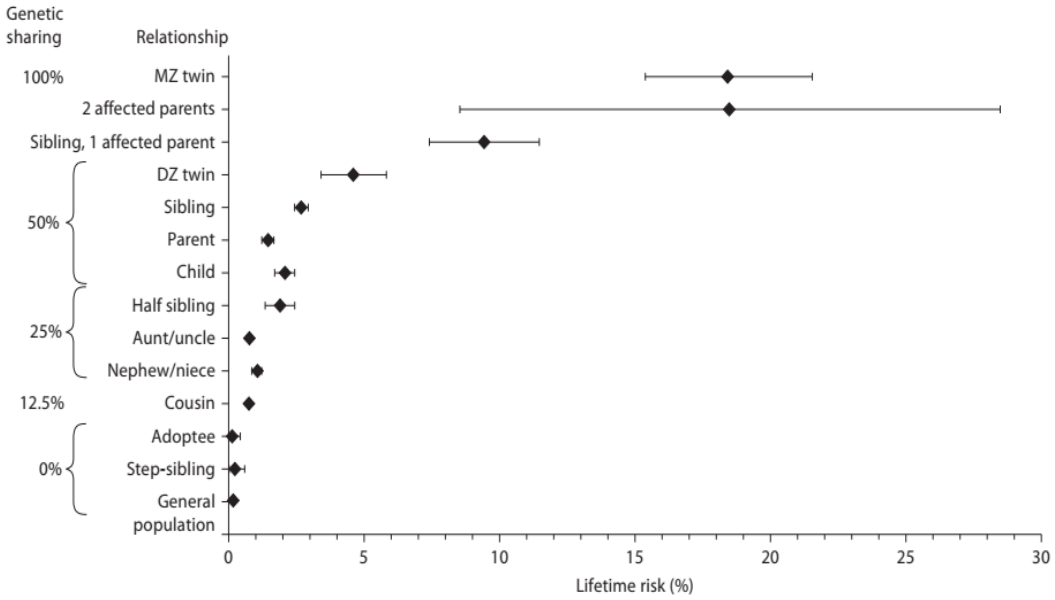
Γενετική της ΣΚΠ

Established multiple sclerosis risk alleles in the major histocompatibility complex

	OR
*HLA-DRB1*15:01*	3·10
*HLA-A*02:01*	1·37†
*HLA-DRB1*03:01–DQB1*02:01*	1·26
*HLA-DRB1*13:03–DQB1*03:01*	2·40
rs9277535_G‡	1·28

Lancet Neurol 2014; 13: 700–09

Population-based prevalence rates in relatives of MS probands

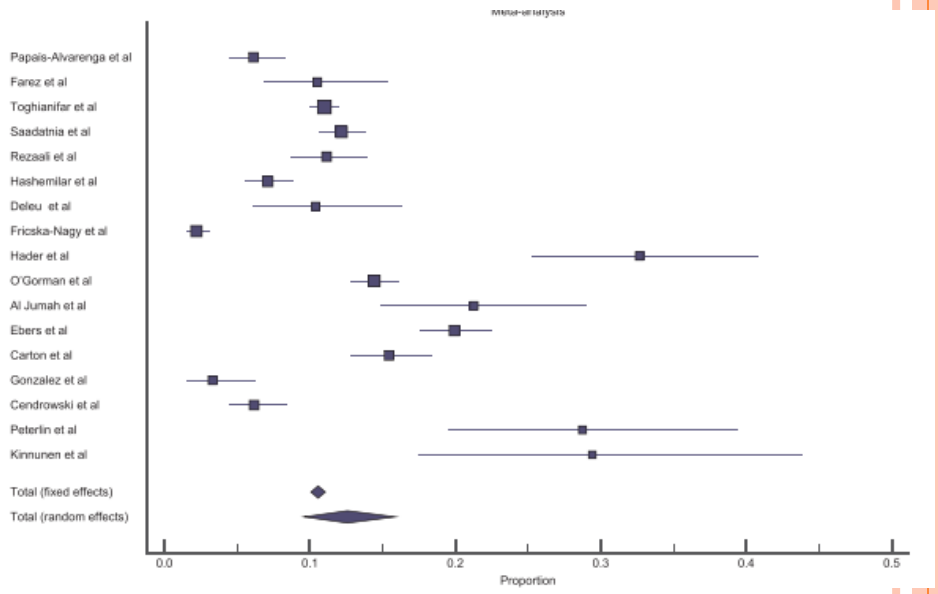


Multiple sclerosis is a complex neurological disease, with 20% of risk heritability attributable to common genetic variants, including >230 identified by genome-wide association studies

Lancet Neurol 2008; 7: 268–77

Worldwide prevalence of familial MS A systematic review and meta-analysis

- **The prevalence of FMS was estimated as 12.6%** within a total sample size of 14,619 MS patients in the world as of 95% confidence interval (CI: 9.6–15.9)
- We detected significant heterogeneity from Hungary to Saskatchewan for FMS prevalence that was not latitude and ethnicity dependent. This highlighted the accumulation effects of genetic and environment on FMS prevalence.



Multiple Sclerosis and Related Disorders 20 (2018) 43–47

Established and possible lifestyle and environmental risk factors for MS

Factor	OR	HLA gene interaction	Combined OR (nongenetic factor + HLA allele)	Effect during adolescence	Immune system implied	Level of evidence
Smoking	~1.6	Yes	14	No	Yes	+++
EBV infection (seropositivity)	~3.6	Yes	~15	Yes	Yes	+++
Vitamin D level <50 nM	~1.4	No	NA	Probably	Yes	+++
Adolescent obesity (BMI >27 at age 20 years)	~2	Yes	~15	Yes	Yes	+++
CMV infection (seropositivity)	0.7	No	NA	Unknown	Yes	++
Night work	~1.7	No	NA	Yes	Yes	++
Low sun exposure	~2	No	NA	Probably	Yes	++
Infectious mononucleosis	~2	Yes	7	Yes	Yes	++
Passive smoking	~1.3	Yes	6	No	Yes	+
Organic solvent exposure	~1.5	Unknown	Unknown	Unknown	Unknown	+
Oral tobacco/nicotine	0.5	No	NA	Unknown	Yes	+
Alcohol	~0.6	No	NA	Unknown	Yes	+
Coffee	~0.7	No	NA	Unknown	Yes	+

Nat Rev Neurol. 2017 Jan;13(1):25-36

MS IS A PREDOMINANTLY WHITE MATTER DISEASE (?)

MYELO-CORTICAL MS

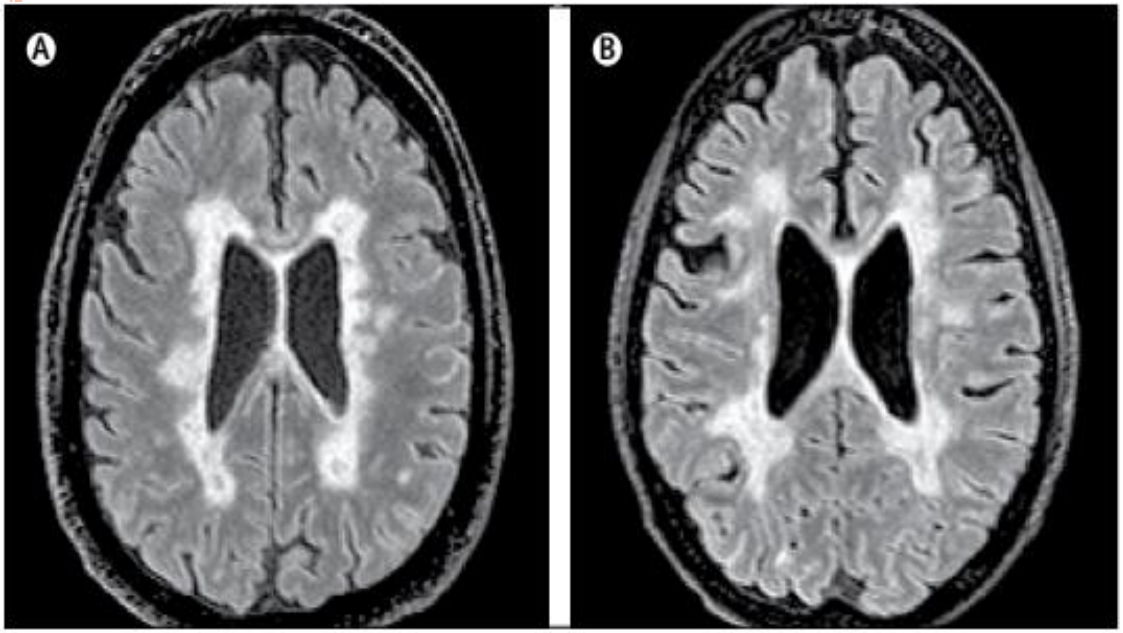
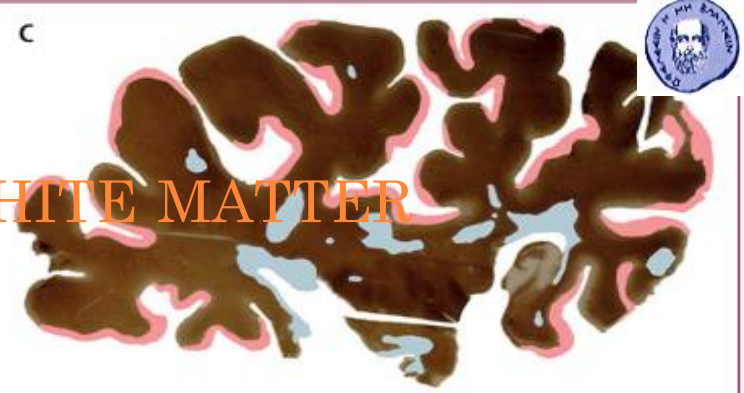
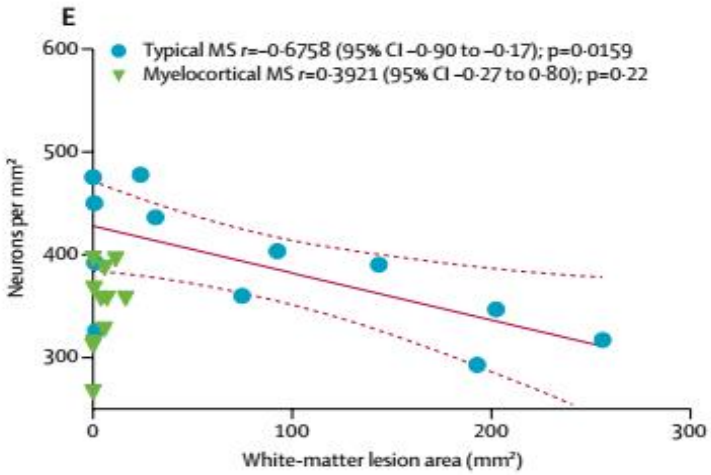
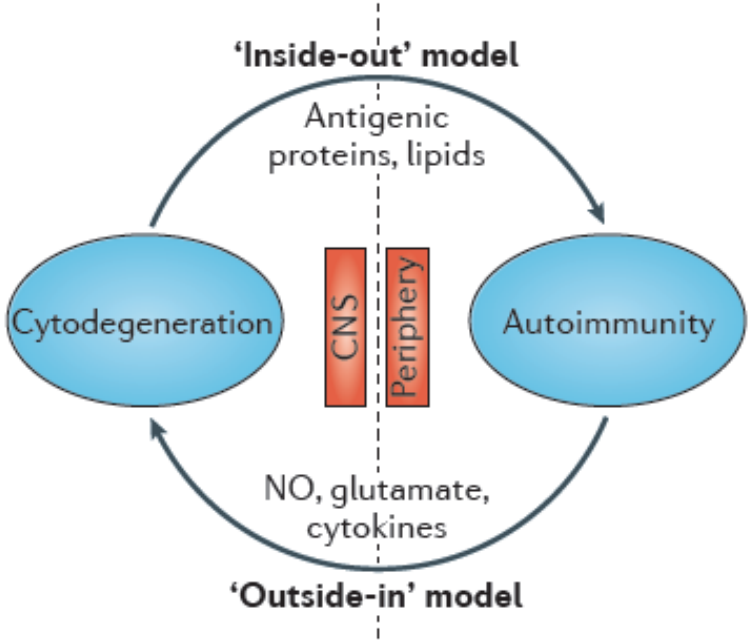


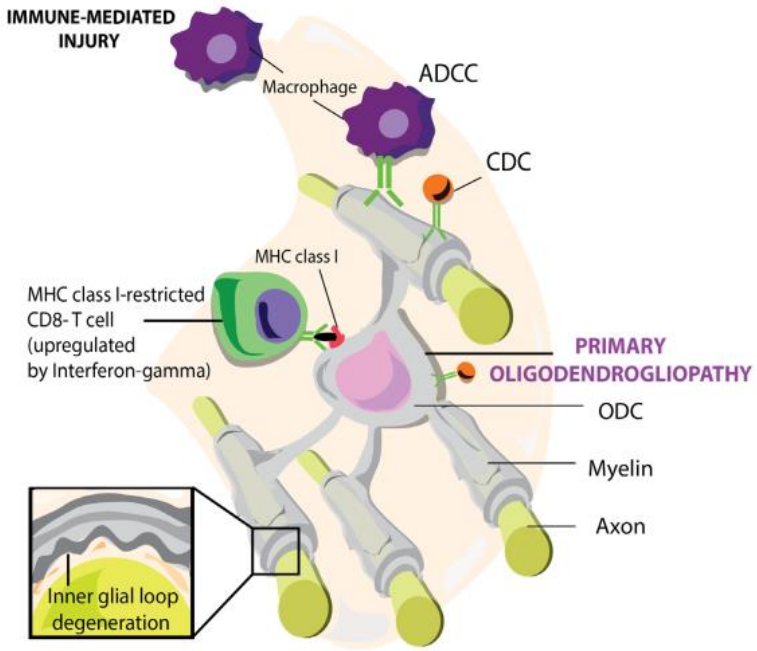
Figure 3: **MRI in myelocortical multiple sclerosis and typical multiple sclerosis**
Representative T2-weighted, fluid-attenuated inversion recovery images post-mortem from brains of individuals with typical multiple sclerosis (A) and myelocortical multiple sclerosis (B).



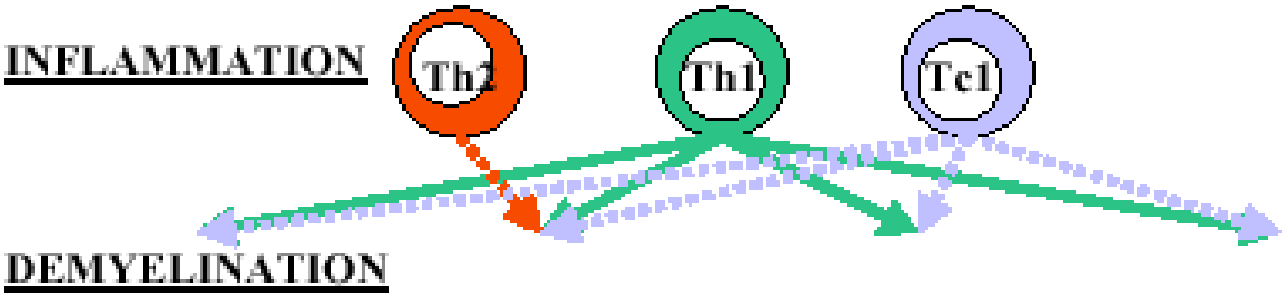


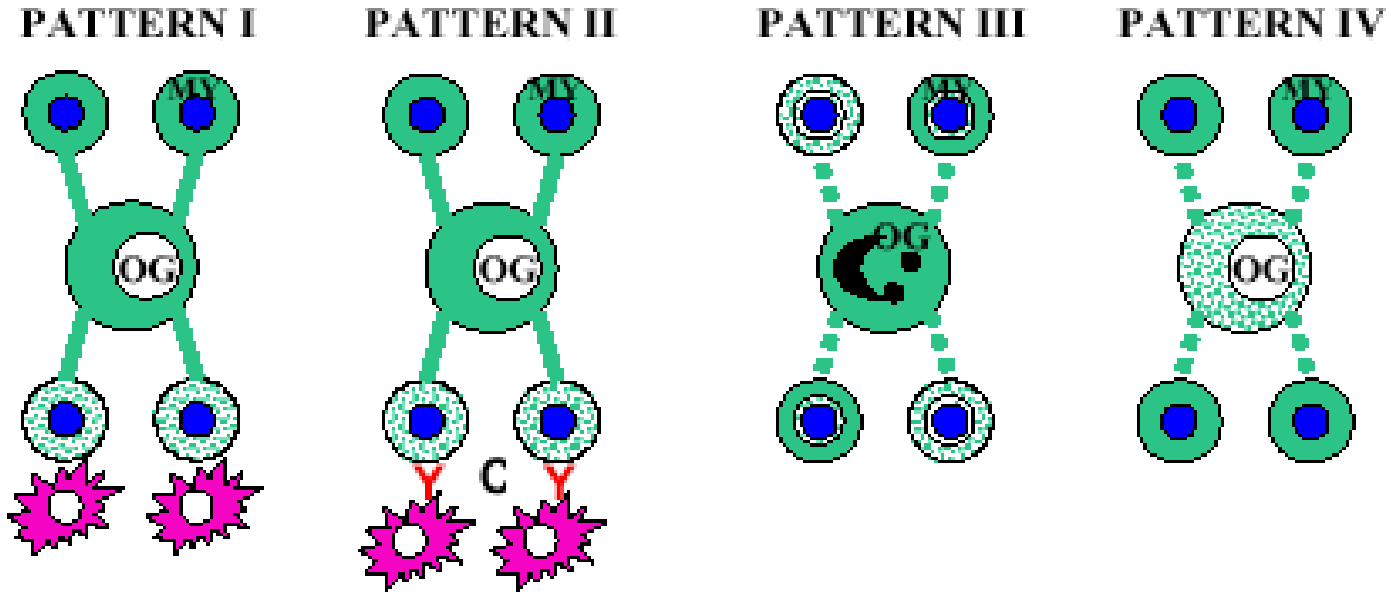
Neyrodegeneration and inflamation Which comes first?





PATHOLOGY OF MULTIPLE SCLEROSIS





Luchinetti C et al, AAN 2001

Η ΤΟΠΟΓΡΑΦΊΑ ΤΗΣ ΑΠΟΜΥΕΛΊΝΩΣΗΣ ΚΑΙ ΝΕΥΡΟΕΚΦΎΛΙΣΗΣ ΣΤΟΝ ΕΓΚΈΦΑΛΟ ΤΩΝ ΑΣΘΕΝΏΝ ΜΕ ΣΚΠ

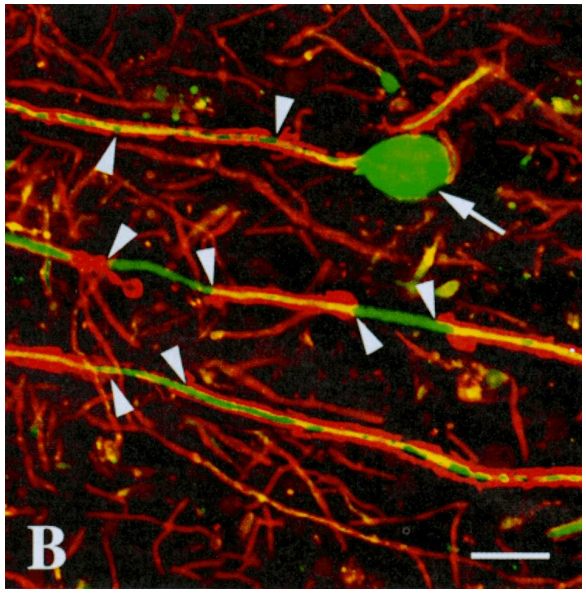
- Η φλοιϊκή απομυελίνωση σχετίζεται με φλεγμονώδεις διηθήσεις στην μήνιγγες πιο εκσεσημασμένες στις αύλακες και πιθανόν υποβοηθείται από την χαμηλή ροή του ΕΝΥ στις περιοχές αυτές.
- Οι εστιακές απομυελινωτικές βλάβες της λευκής ουσίας συμβαίνουν σε περιοχές υψηλής φλεβικής πυκνότητας και συσσωρεύονται σε μεθοριακές (watershed) περιοχές αιμάτωσης.
- Δύο διαφορετικά πρότυπα νευροεκφύλισης αναγνωρίστηκα στον φλοιό
  - Οξειδωτική βλάβη των φλοιϊκών νευρώνων: σχετίζεται με την παρακείμενη φλεγμονή των μηνίγγων –πλέον εκσεσημασμένη στις φλοιϊκές εστίες με ενεργό απομυελίνωση
  - Ανάδρομη (retrograde) νευροεκφύλιση συσχετίστηκε με τις απομυελινωτικές εστίες και την αξονικη βλάβη στη λευκή ουσία

Haider BRAIN 2016: 139; 807–815

Axonal Loss Begins at Disease Onset

Based on magnetic resonance and morphologic studies:

- Evidence that axonal loss/cerebral atrophy occurs early, at a time when no or only mild disability is present [1,2]
- Evidence that progressive disability reflects cumulative and irreversible axonal loss [3,4]
- Axonal damage may occur more rapidly at the early stage of the disease [1,5]
- Suggestion that axonal loss can occur independently of demyelination [6]



Trapp et al., NEJM 338, 278 (1998)

[1]De Stefano et al. 2001, [2]Simon et al. 1999, [3]Bjartmar & Trapp 2001,
[4]Trapp et al. 1998, [5]Liu et al. J Neurol Neurosurg Psychiatr 1999, [6]Bjartmar et al. 2001

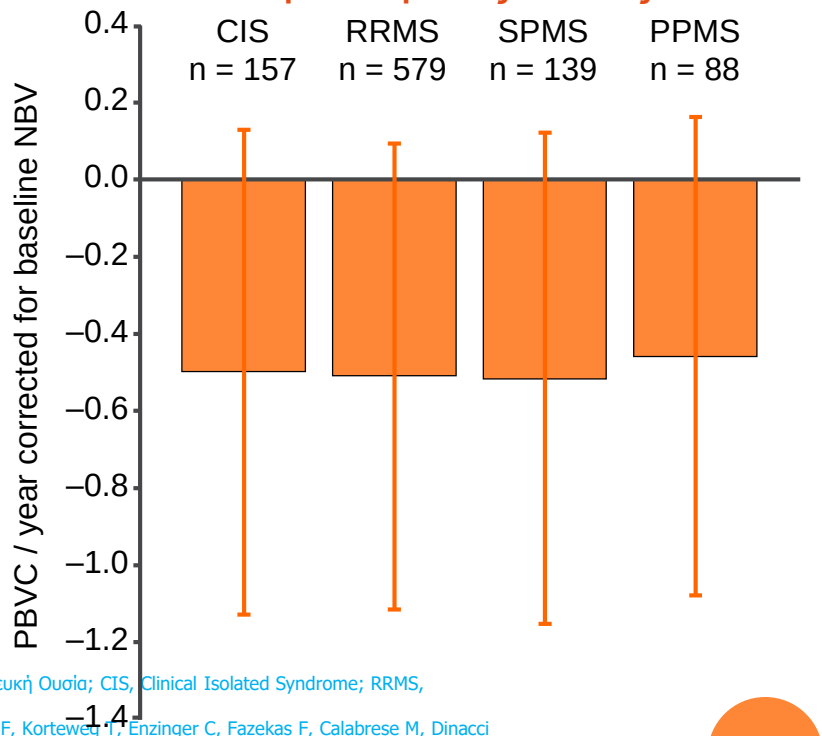
ΔΙΑΧΥΤΕΣ ΒΛΑΒΕΣ

ΡΥΘΜΟΣ ΜΕΙΩΣΗΣ ΕΓΚΕΦΑΛΙΚΟΥ ΟΓΚΟΥ

Σημαντικές μεταβολές της NAWM και της GM εμφανίζουν συσχέτιση με προοδευτική μείωση εγκεφαλικού όγκου[1]

- **Μείωση εγκεφαλικού όγκου στη ΠΣ συμβαίνει:**
  - τόσο στην GM όσο και στην WM[2]
  - πρώιμα και στη διάρκεια όλων των φάσεων και των υποτύπων της νόσου
  - με 3 ως 5 φορές ταχύτερο ετήσιο ρυθμό σε άτομα με ΠΣ έναντι υγιών μαρτύρων[3-6]
    - ασθενείς με ΠΣ: 0.5–1.35%[3-5]
    - υγιείς μάρτυρες: 0.2–0.4%[3,6,7]

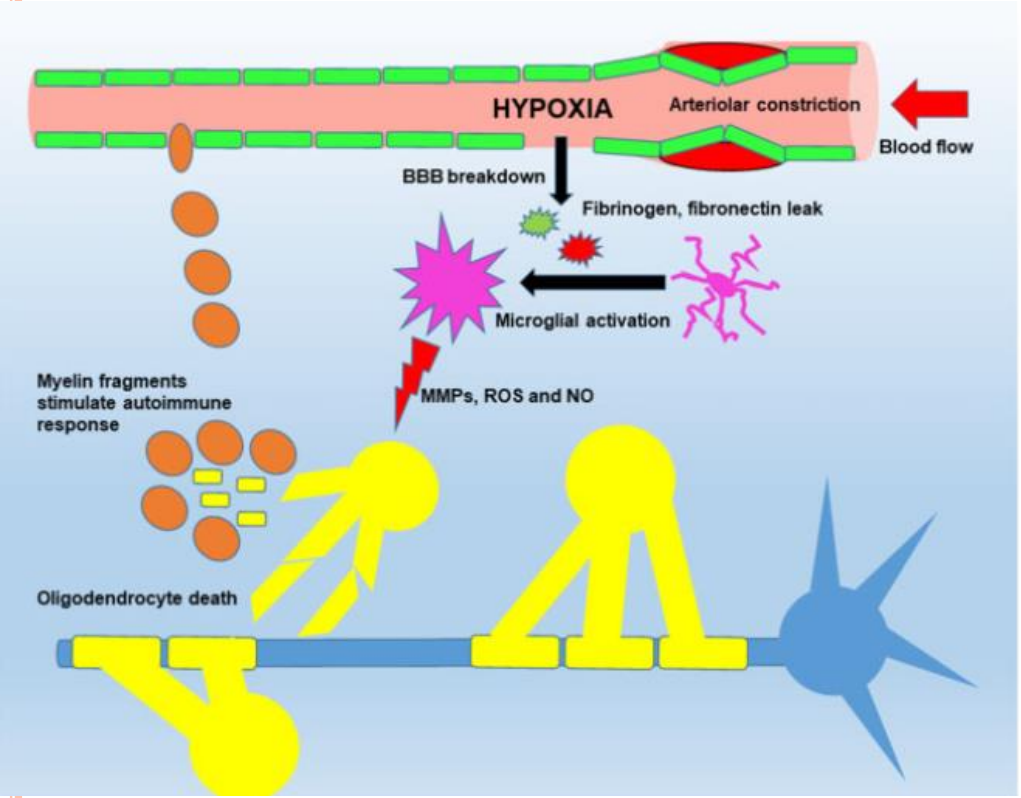
Ευρωπαϊκή πολυκεντρική αναδρομική μελέτη του ρυθμού ατροφίας 1 έτους σε μη θεραπευόμενους ασθενείς[8]



ΠΣ, Πολλαπλή Σκλήρυνση; WM, Λευκή Ουσία; GM, Φαιά Ουσία; NAWM, Φαινομενικά-Φυσιολογική Λευκή Ουσία; CIS, Clinical Isolated Syndrome; RRMS, Relapsing-Remitting MS; SPMS, Secondary Progressive MS; PPMS, Primary Progressive MS

Reproduced with permission. De Stefano N, Giorgio A, Battaglini M, Rovaris M, Sormani MP, Barkhof F, Korteweg T, Enzinger C, Fazekas F, Calabrese M, Dinacci D, Tedeschi G, Gass A, Montalban X, Rovira A, Thompson A, Comi G, Miller DH, Filippi M. Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes. *Neurology* 2010; 74(23): 1868-1876. 1. Kutzelnigg A and Lassmann HY. *Handbook Clin Neurol* 2014; 2. Filippi M *et al. Lancet Neurology* 2012; 3. De Stefano N *et al.* Oral presentation S13.006 at *AAN* 2014; 4. Barkhof F *et al. Nat Rev Neurol* 2009; 5. Bermel RA and Bakshi R. *Lancet Neurol* 2006; 6. Hedman AM *et al. Human Brain Mapping* 2012; 7. Enzinger C *et al. Neurology* 2005; 8. De Stefano N *et al. Neurol* 2010

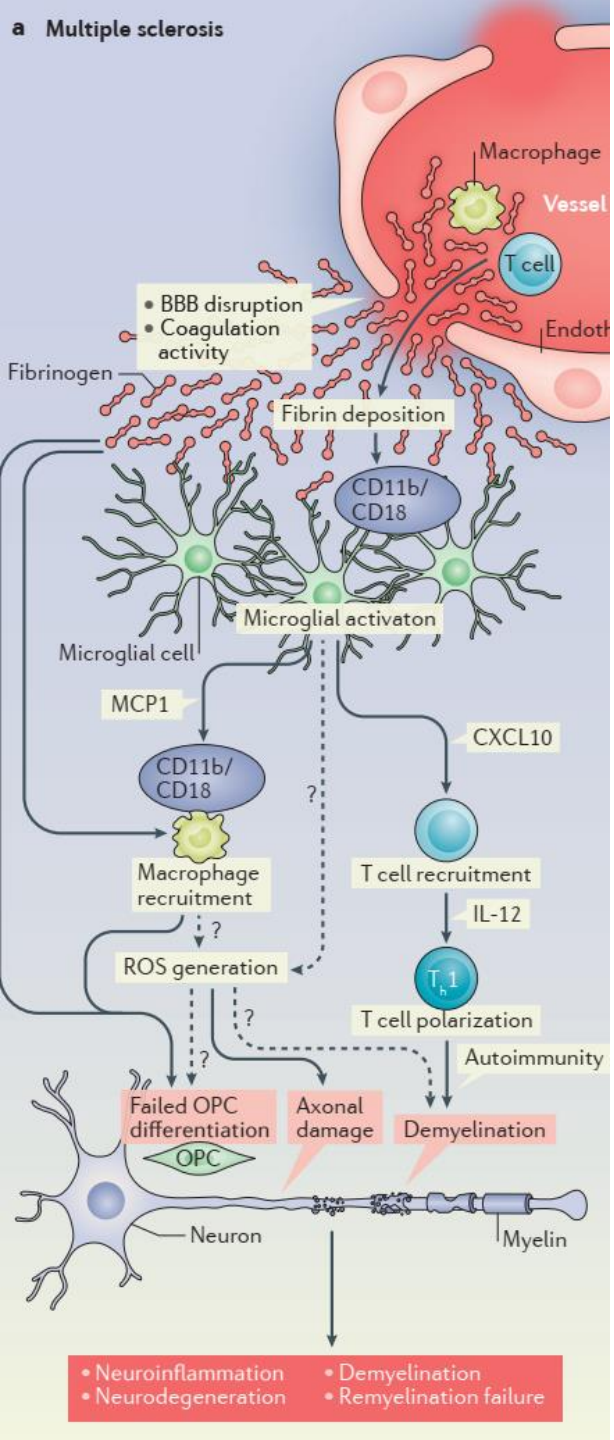
HYPOXIA IN MULTIPLE SCLEROSIS IS IT THE CHICKEN OR THE EGG?



Cerebrovascular dysfunction leads to hypoperfusion, triggering a transient hypoxic state in vulnerable areas of the CNS (vascular watershed areas), which results in blood–brain barrier (BBB) disruption and localized leak of serum proteins (fibrinogen, fibronectin and vitronectin) leading to microglial activation. The activated microglia then release cytotoxic factors (cytokines, MMPs, ROS and NO), which damage oligodendrocytes, leading to cell death and demyelination. This, in turn, triggers release of myelin antigenic fragments that stimulate T lymphocytes on surveillance, leading ultimately to a full-blown autoimmune response

BRAIN 2021: 144; 402–410

Fibrinogen in MS



In multiple sclerosis animal models, blood–brain barrier (BBB) disruption leads to increased coagulation activity and fibrin deposition in the brain, which binds to the CD11b/CD18 integrin receptor, thus driving early microglial activation, recruitment of peripheral macrophages and T cells and leading to demyelination and axonal damage. Fibrin-induced activation induces a gene transcription signature characterized by increased secretion of chemokines (such as CXC-chemokine ligand 10 (CXCL10) and monocyte chemoattractant protein 1 (MCP1)) to promote recruitment of T cells, increased antigen presentation and release of instructive signals (such as interleukin 12 (IL-12)) for inducing T helper 1 (TH1) cell differentiation to promote autoimmunity and demyelination. In parallel, perivascular microglia cluster at sites of fibrin deposition, which correlate with areas of reactive oxygen species (ROS) generation and axonal damage in vivo. Mechanisms and consequences of fibrin-induced ROS release in the CNS are not known (dotted lines). Fibrinogen also blocks oligodendrocyte progenitor cell (OPC) differentiation to myelinating cells by direct and immune-mediated mechanism

doi:10.1038/nrn.2018.13

White Matter and Deep Gray Matter Hemodynamic Changes in Multiple Sclerosis Patients with Clinically Isolated Syndrome

Efrosini Z. Papadaki,[1*] Vasileios C. Mastorodemos,[2] Emmanouil Z. Amanakis,[1] Konstantinos C. Tsekouras,[1] Antonis E. Papadakis,[3] Nikolaos D. Tsavalas,[1] Panagiotis G. Simos,[4] Apostolos H. Karantanas,[1] Andreas Plaitakis,[2] and Thomas G. Maris[3]

❖All measured normal appearing white matter and DGM regions of the patients with CIS had significantly higher cerebral blood volume and mean transit time values, while averaged DGM regions had significantly lower CBF values, compared to those of normal volunteers ($P < 0.001$).

❖Regarding patients with RRMS,all measured normal appearing white matter and DGM regions showed lower CBF values than those of normal volunteers and lower cerebral blood volume and CBF values compared to patients with CIS ($P < 0.001$).

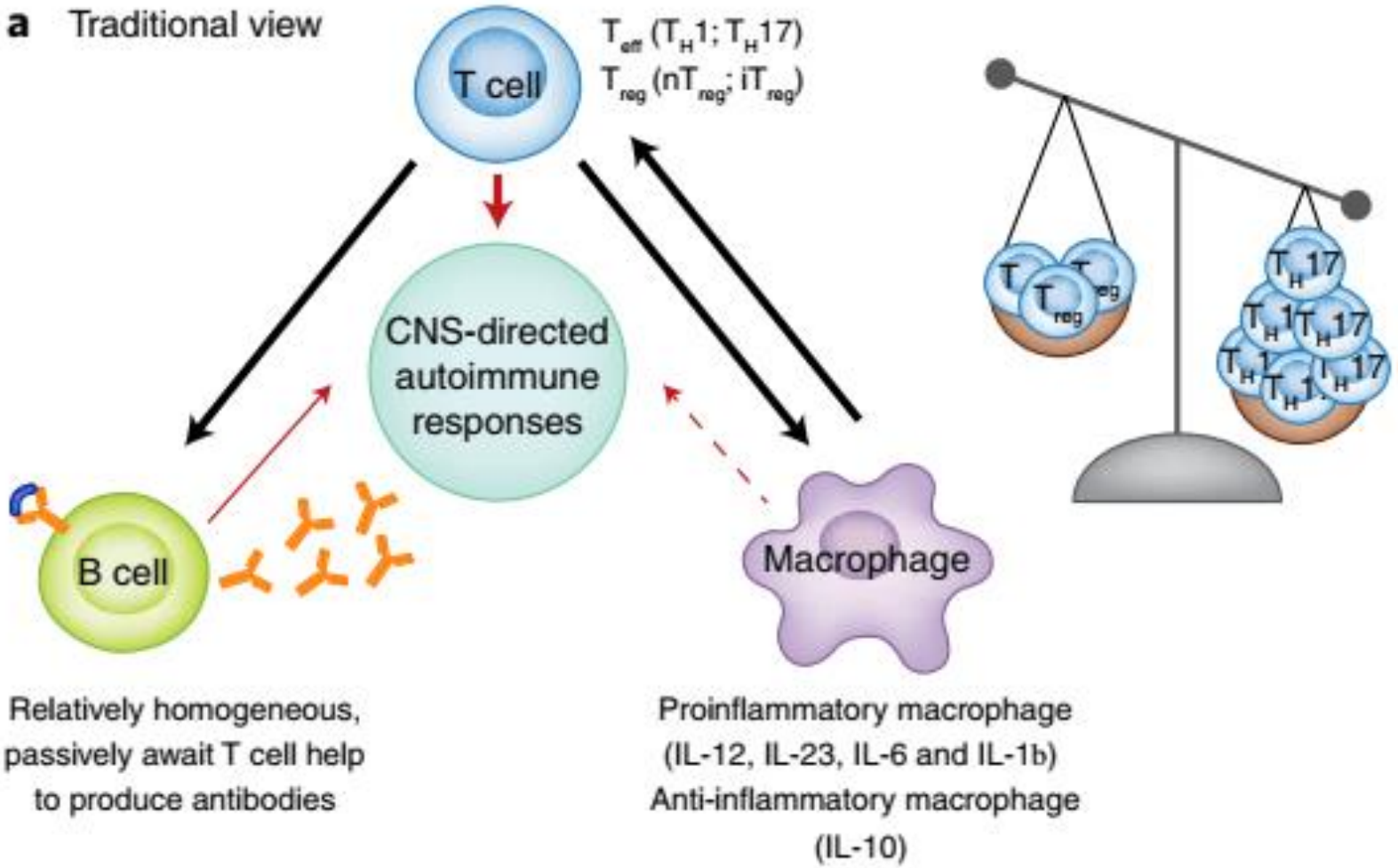
European Journal of Neurology 2014, **21:** 499–505 doi:10.1111/ene.12338

Hemodynamic evidence linking cognitive deficits in clinically isolated syndrome to regional brain inflammation

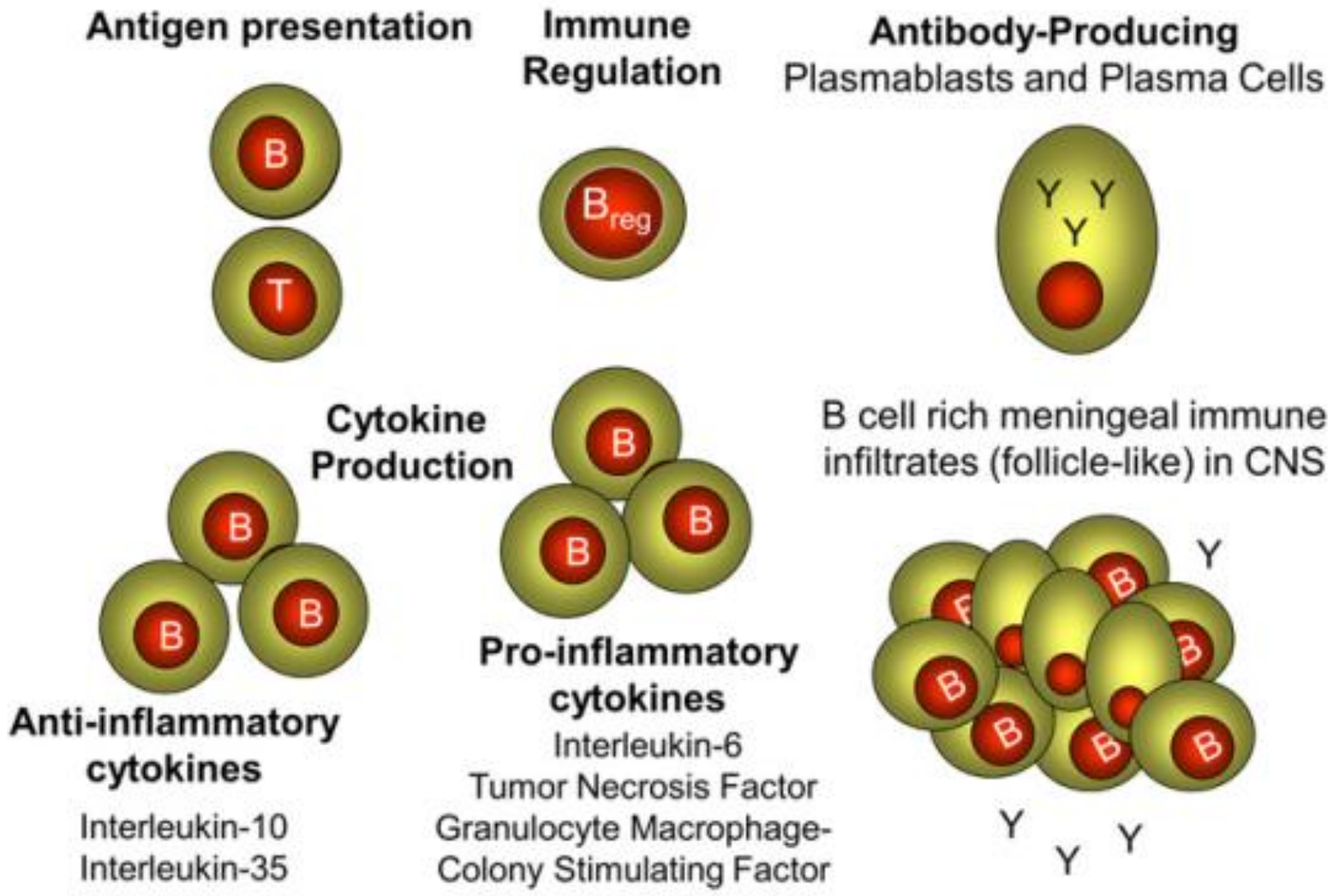
E. Z. Papadaki[a], P. G. Simos[b], T. Panou[c], V. C. Mastorodemos[c], T. G. Maris[d], A. H. Karantanas[a] and A. Plaitakis[c]

- Verbal memory in CIS correlates inversely with elevated CBV values of brain structures involved in memory.

ΜΟΝΤΕΛΟ ΠΑΘΟΓΕΝΕΣΗΣ MS
a T-cell mediated disease?

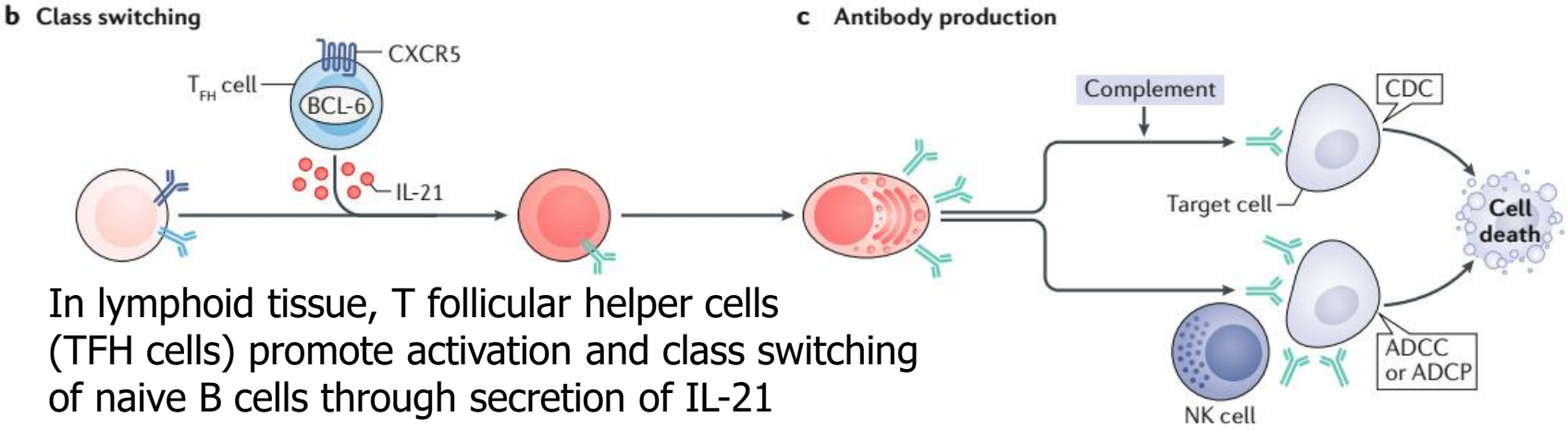


B CELL FUNCTIONS

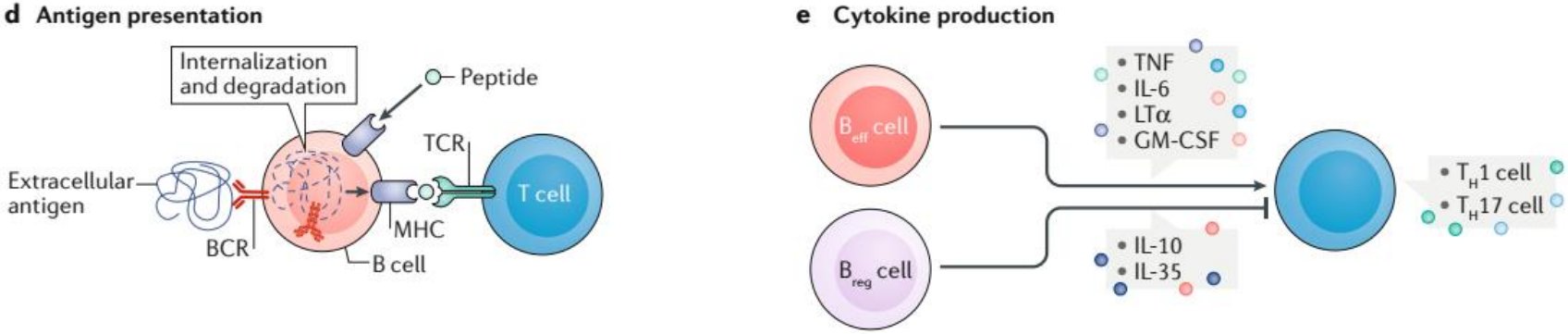


D. Baker et al. / EBioMedicine 16 (2017) 41–50

B CELL FUNCTIONS



In lymphoid tissue, T follicular helper cells (TFH cells) promote activation and class switching of naive B cells through secretion of IL-21

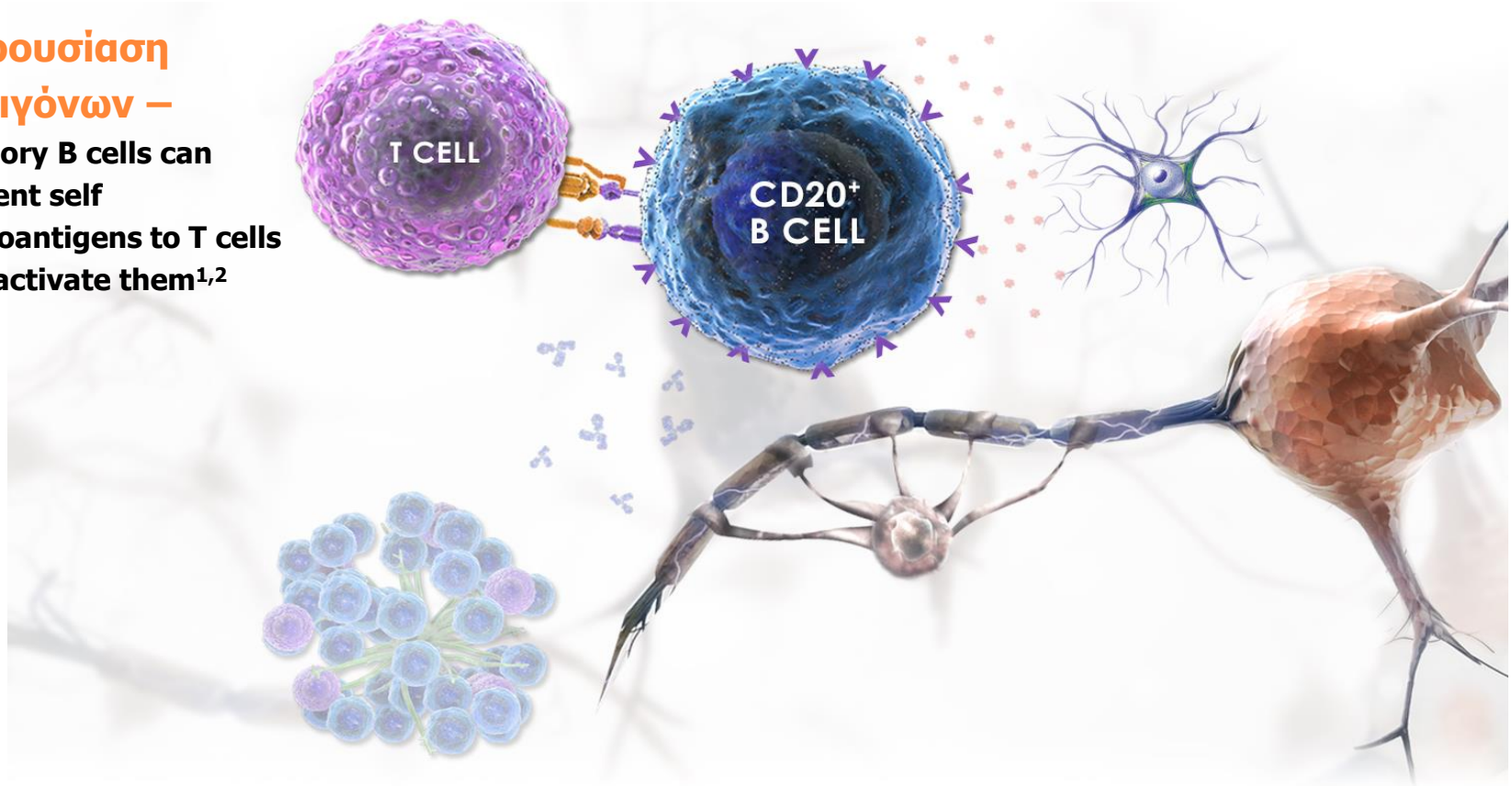


B cells secrete a variety of proinflammatory cytokines, leading to type 1 T helper cell (TH1 cell) or IL-17-secreting T helper cell (TH17 cell) polarization. (B reg cells also secrete anti-inflammatory cytokines, including IL-10 and IL-35,

Τα Β Κύτταρα Μπορούν να Συμβάλλουν στην Παθοφυσιολογία και στην Ενεργότητα της ΠΣ με Διαφορετικούς Μηχανισμούς:

Παρουσίαση Αντιγόνων –

Memory B cells can present self neuroantigens to T cells and activate them[1,2]



1. Crawford A, *et al. J Immunol* 2006;176:3498–506. **2.** Bar-Or A, *et al. Ann Neurol* 2010;67:452–61.
3. Lisak RP, *et al. J Neuroimmunol* 2012;246(1-2):85–95. **4.** Weber MS, *et al. Biochim Biophys Acta* 2011;1812:239–45.
5. Serafini B, *et al. Brain Pathol* 2004;14:164–74. **6.** Magliozzi R, *et al. Ann Neurol* 2010;68:477–93.

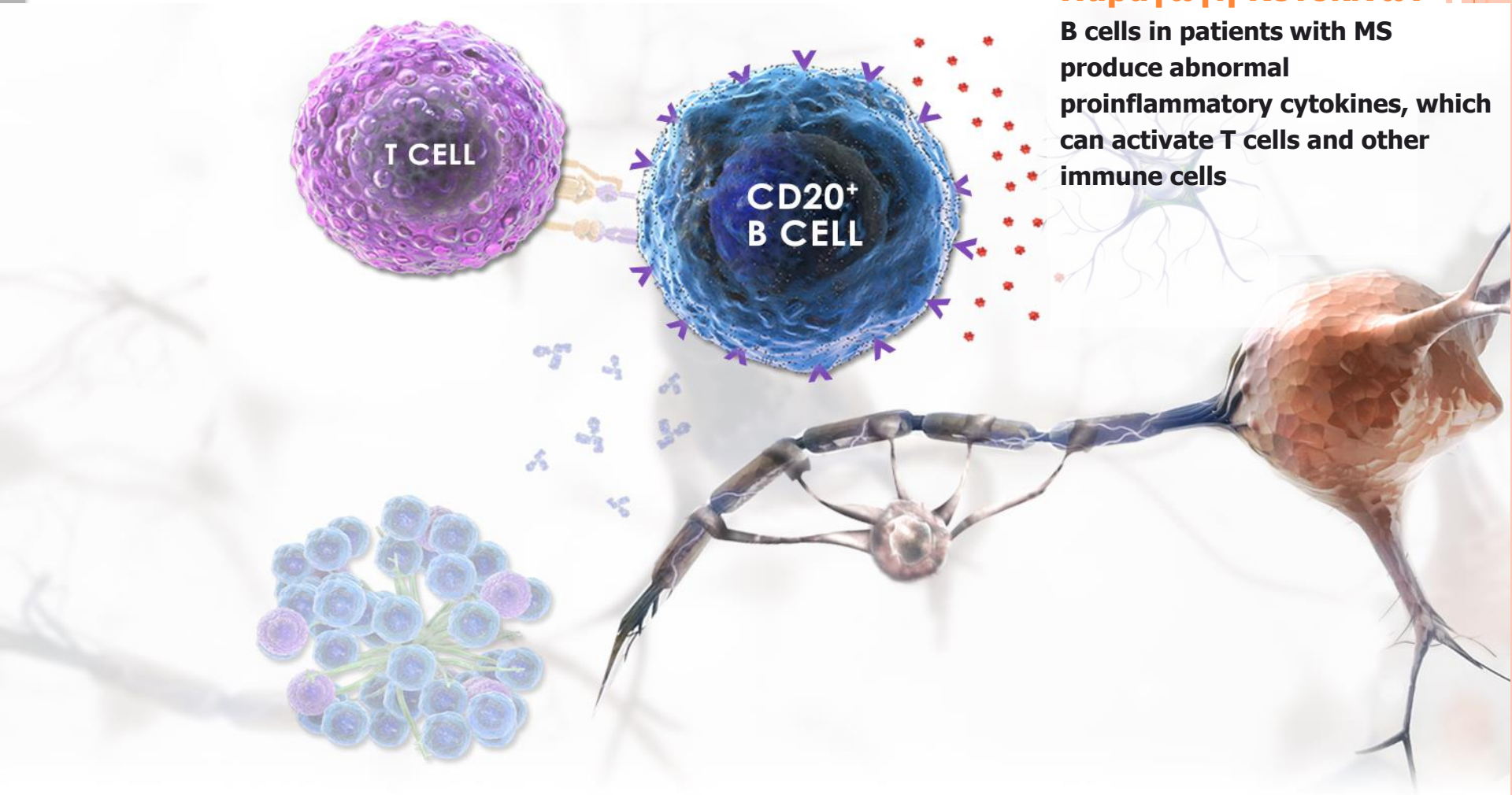
APC ROLE OF B CELLS

- B cells can recognize three-dimensional 'conformational' epitope (vs professional APCs linear epitope)
- B cells are particularly effective APCs when they recognize the same antigen as T cells
- Human B cells express co-stimulatory molecules CD80/86
- B cells express co-inhibitory molecules involved in downregulating the responses of effector T cells such as Programmed cell death-1 (PD-1)/PD-L1 and GITRL (glucocorticoid-induced TNFR) ligands

Τα Β Κύτταρα Μπορούν να Συμβάλλουν στην Παθοφυσιολογία και στην Ενεργότητα της ΠΣ με Διαφορετικούς Μηχανισμούς:

Παραγωγή Κυτοκινών[2,3]

B cells in patients with MS produce abnormal proinflammatory cytokines, which can activate T cells and other immune cells



3. Lisak RP, *et al. J Neuroimmunol* 2012;246(1-2):85–95. 4. Weber MS, *et al. Biochim Biophys Acta* 2011;1812:239–45.
5. Serafini B, *et al. Brain Pathol* 2004;14:164–74. 6. Magliozzi R, *et al. Ann Neurol* 2010;68:477–93.

B cell Cytokine Production

- B cells (particularly memory B cells) from individuals with MS, compared with healthy control individuals, can be activated to produce abnormally high amounts of the cytokines TNF, LTα, IL-6 and GM-CSF (= Granulocyte-macrophage colony-stimulating factor)
- B cell IL-6 is particularly involved in the generation of type 17 helper T cell (TH17) responses
- after aCD20 therapy, in most patients, reconstituting B cells are CD27– (naive) and produce less proinflammatory cytokines (TNF, LT, IL-6 and GM-CSF) but higher levels of IL-10
- B cells can also downregulate immune responses through the secretion of anti-inflammatory cytokines (including IL-10, TGF-ß and IL-35)

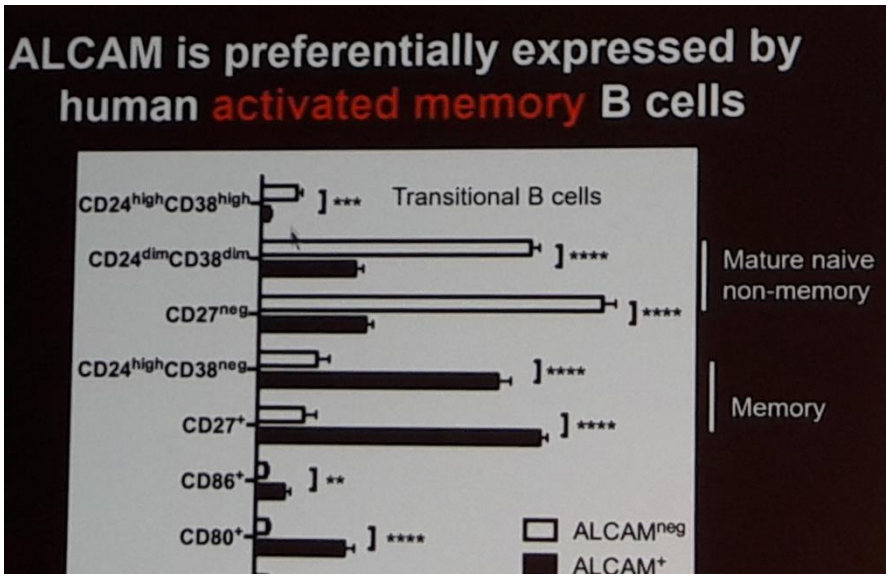
Proinflammatory GM-CSF–producing B cells in MS and B cell depletion therapy

- Proinflammatory GM-CSF–producing human B cell subset that coexpresses high levels of TNFa as well as IL-6, induces proinflammatory myeloid cell activation in a GM-CSF–dependent manner, and is abnormally increased in patients with MS
- In vivo, BCDT resulted in a GM-CSF– dependent decrease in proinflammatory myeloid responses of MS patients.
- Abnormally increased phosphorylation of STAT5 and STAT6 in the B cells of individuals with MS is associated with elevated production of GM-CSF and diminished production of IL-10, whereas dual STAT5–STAT6 signaling blockade during activation reverses the abnormal cytokine response profile of MS B cells
- STAT5/6 signaling was enhanced in B cells of untreated MS patients compared with healthy controls, and B cells reemerging in patients after BCDT normalized their STAT5/6 signaling as well as their GM-CSF/IL-10 cytokine secretion ratios. The diminished proinflammatory myeloid cell responses observed after BCDT persisted even as new B cells reconstituted

Sci. Transl. Med. **7**, 310ra166 (2015)

Activated leukocyte cell adhesion molecule regulates B lymphocyte migration across central nervous system barriers

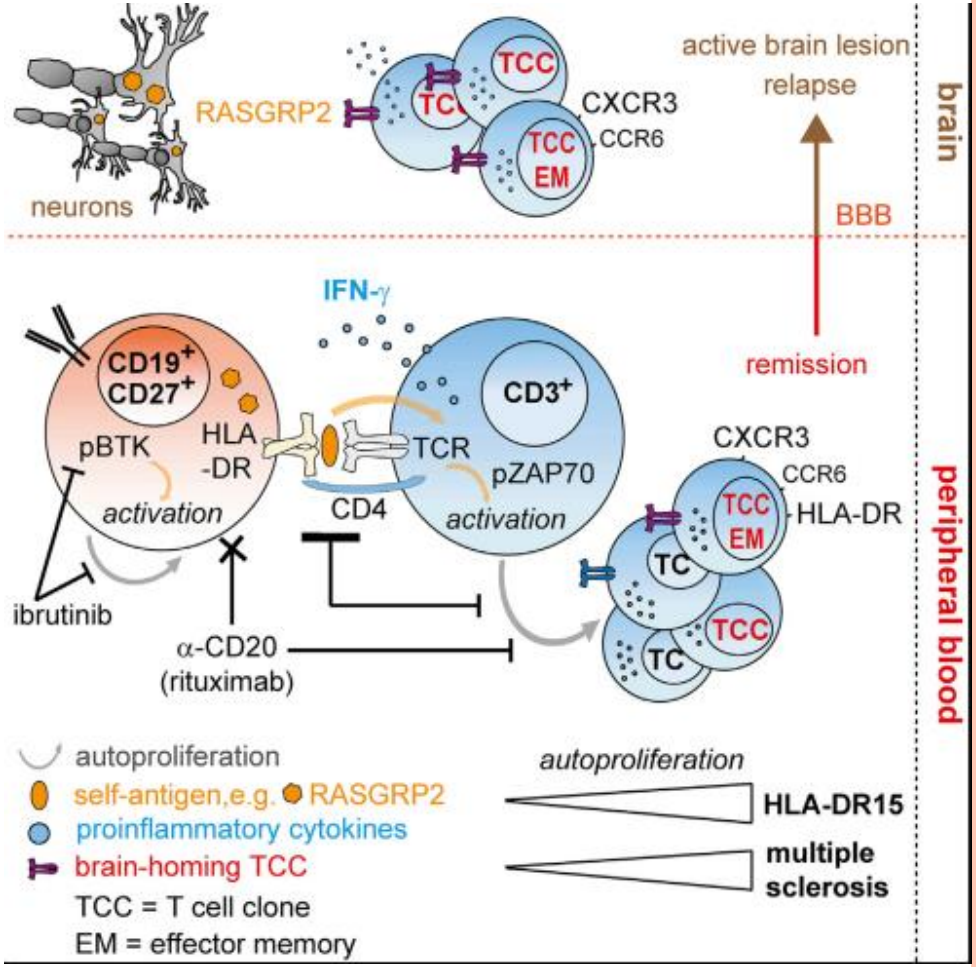
- Activated leukocyte cell adhesion molecule (ALCAM/CD166) identifies subsets of proinflammatory B lymphocytes and drives their transmigration across different CNS barriers in mouse and human.
- Blocking ALCAM alleviated disease severity in animals affected by a B cell–dependent form of experimental autoimmune encephalomyelitis.
- The proportion of ALCAM+ B lymphocytes was increased in the peripheral blood and within brain lesions of patients with MS



Michel *et al.*, *Sci. Transl. Med.* **11**, 2019

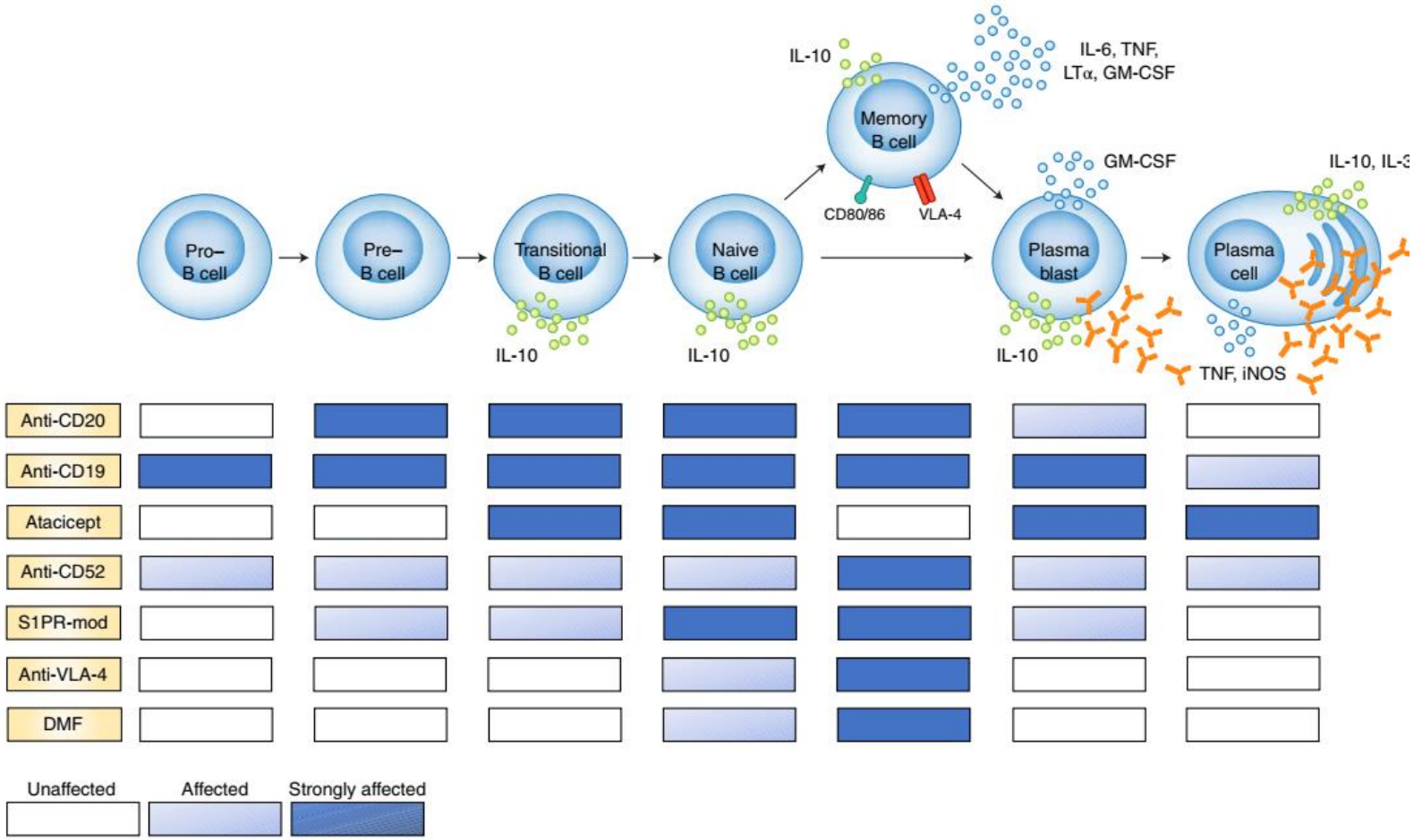
Memory B Cells Activate Brain-Homing, Autoreactive CD4+ T Cells in MS

- The main genetic factor of MS, HLA-DR15, plays a central role in autoproliferation
- Memory B cells drive autoproliferation of Th1 brain-homing CD4+ T cells
- Depletion of B cells in vitro and therapeutically in vivo by antiCD20 effectively reduces T cell autoproliferation
- *in vitro* autoproliferating T cells are enriched for brain-homing T cells.
- Autoproliferating T cells recognize antigens expressed in B cells and brain lesions
- RASGRP2 is a putative target autoantigen that is expressed in the brain and B cells

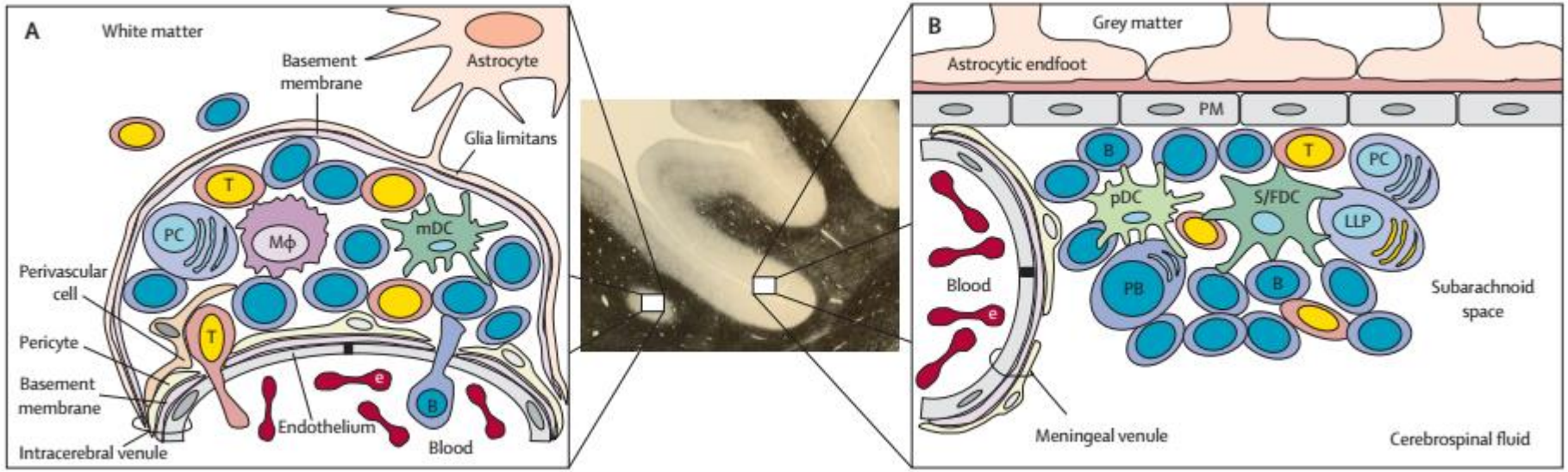


Jelcic et al., 2018, Cell 175, 1–16

Different therapies applied in MS preferentially target distinct cell stages along the B cell lineage

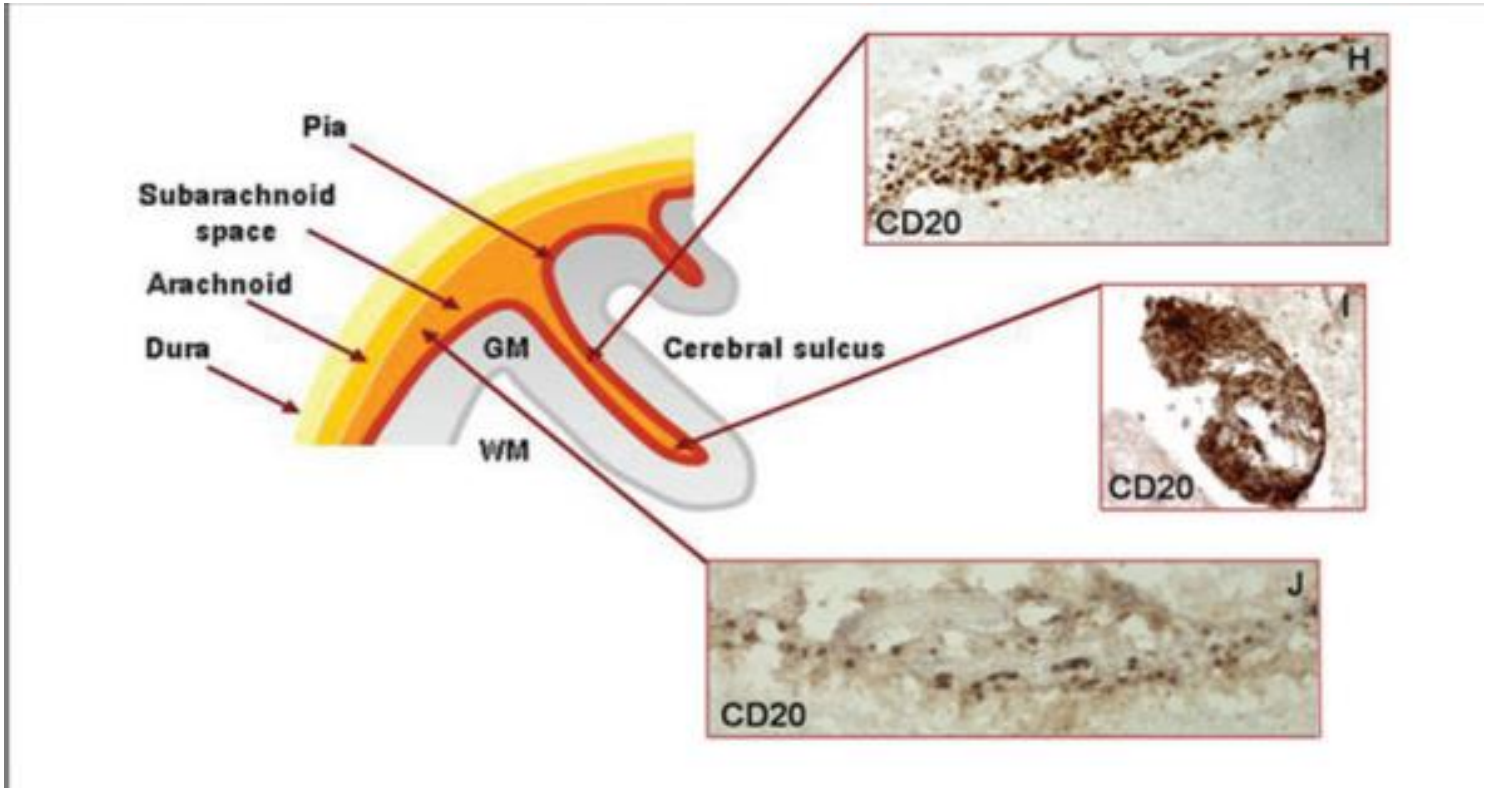


COMPARTMENTALIZED INFLAMMATION
ΔΙΑΜΕΡΙΣΜΑΤΟΠΟΙΗΜΕΝΗ ΦΛΕΓΜΟΝΗ



B cell aggregates are found in the pia mater overlying the cortex in all subtypes of MS. In secondary progressive MS, ectopic follicle-like lymphoid structures containing B cells, plasma cells, T cells and follicular dendritic cells are found along the meningeal pia mater.

COMPARTMENTALIZED INFLAMMATION
ΔΙΑΜΕΡΙΣΜΑΤΟΠΟΙΗΜΕΝΗ ΦΛΕΓΜΟΝΗ



Brain (2007), 130, 1089-1104

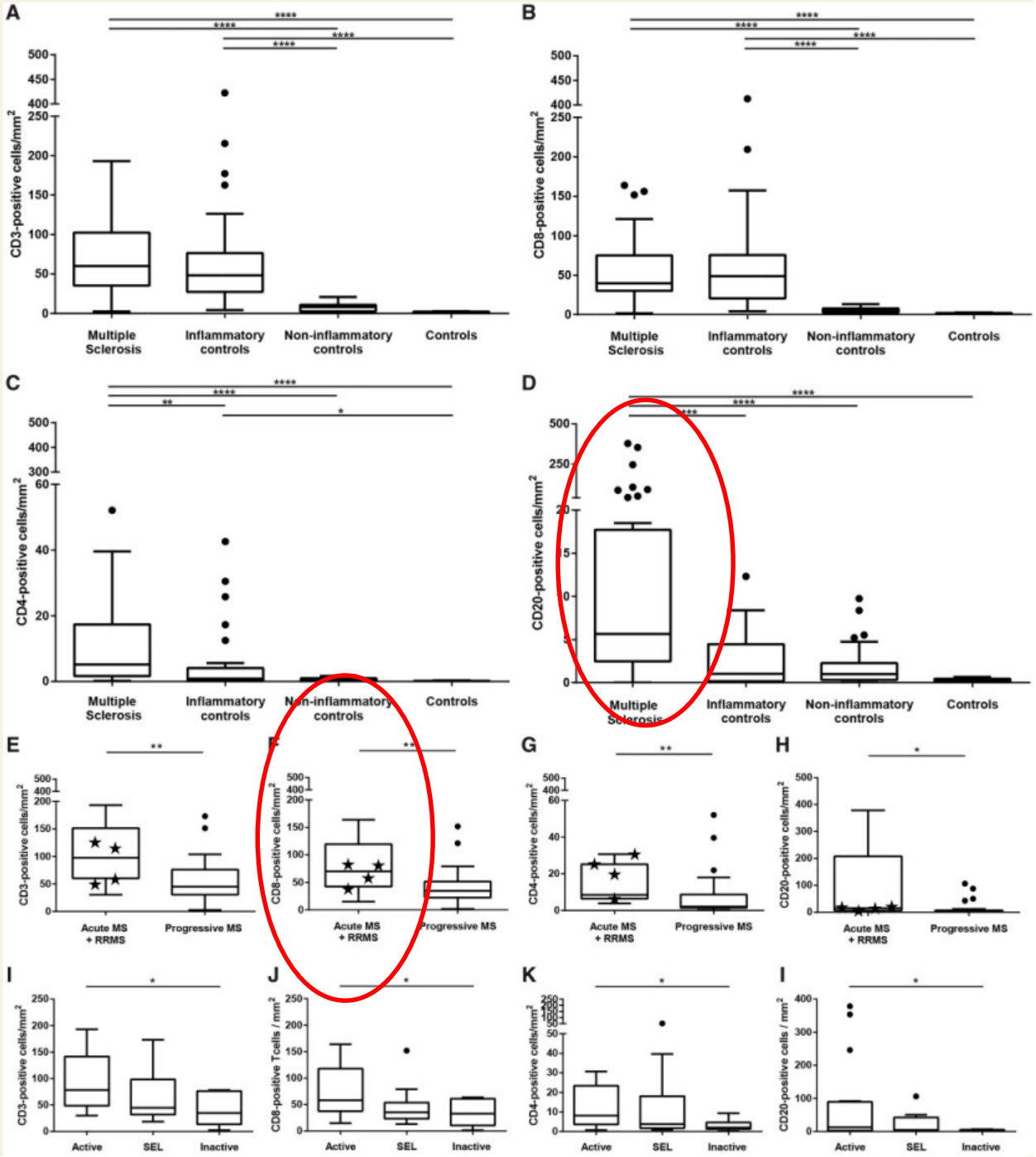
The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8 + T lymphocytes and B cells

- In multiple sclerosis lesions, we found a dominance of CD8 + T cells and a prominent contribution of CD20 + B cells in all disease courses and lesion stages, including acute multiple sclerosis cases with very short disease duration, while CD4 + T cells were sparse

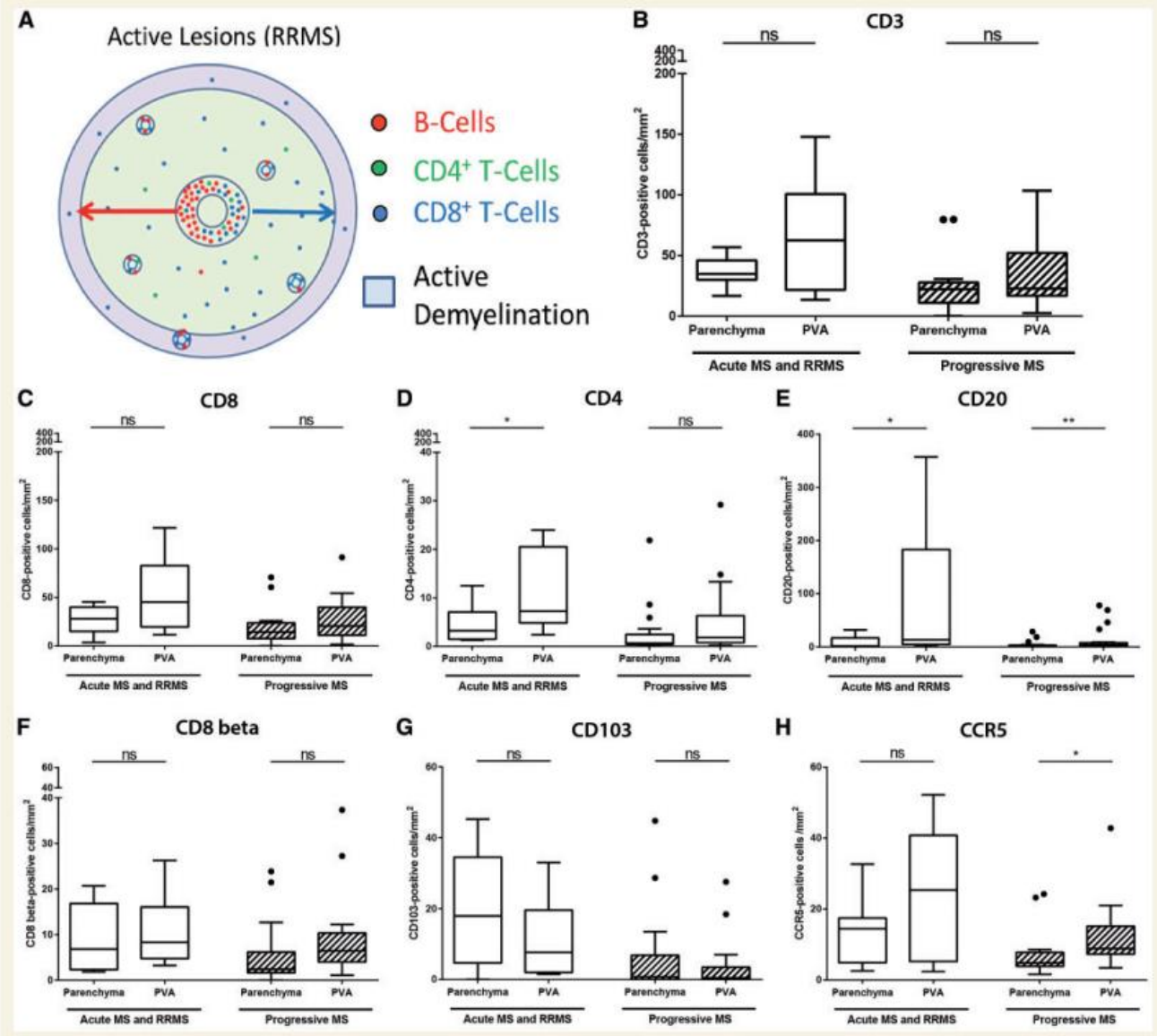
- CD8 + T cells acquire features of tissue-resident memory cells, which may be focally reactivated in active lesions of acute, relapsing and progressive multiple sclerosis, while B cells, at least in part, gradually transform into plasma cells.

- The loss of surface molecules involved in the egress of leucocytes from inflamed tissue, such as S1P1 or CCR7, and the upregulation of CD103 expression may be responsible for the compartmentalization of the inflammatory response in established lesions

BRAIN 2018: 141; 2066–2082


A
CD3-positive cells/mm2
Multiple Sclerosis
Inflammatory controls
Non-inflammatory controls
Controls
B
CD8-positive cells/mm2
C
CD4-positive cells/mm2
D
CD20-positive cells/mm2
E
F
G
H
Acute MS + RRMS
Progressive MS
I
J
K
L
Active
SEL
Inactive
CD8-positive Tcells / mm2

Distribution of leucocytes within different multiple sclerosis lesion areas



BRAIN 2018: 141; 2066–2082

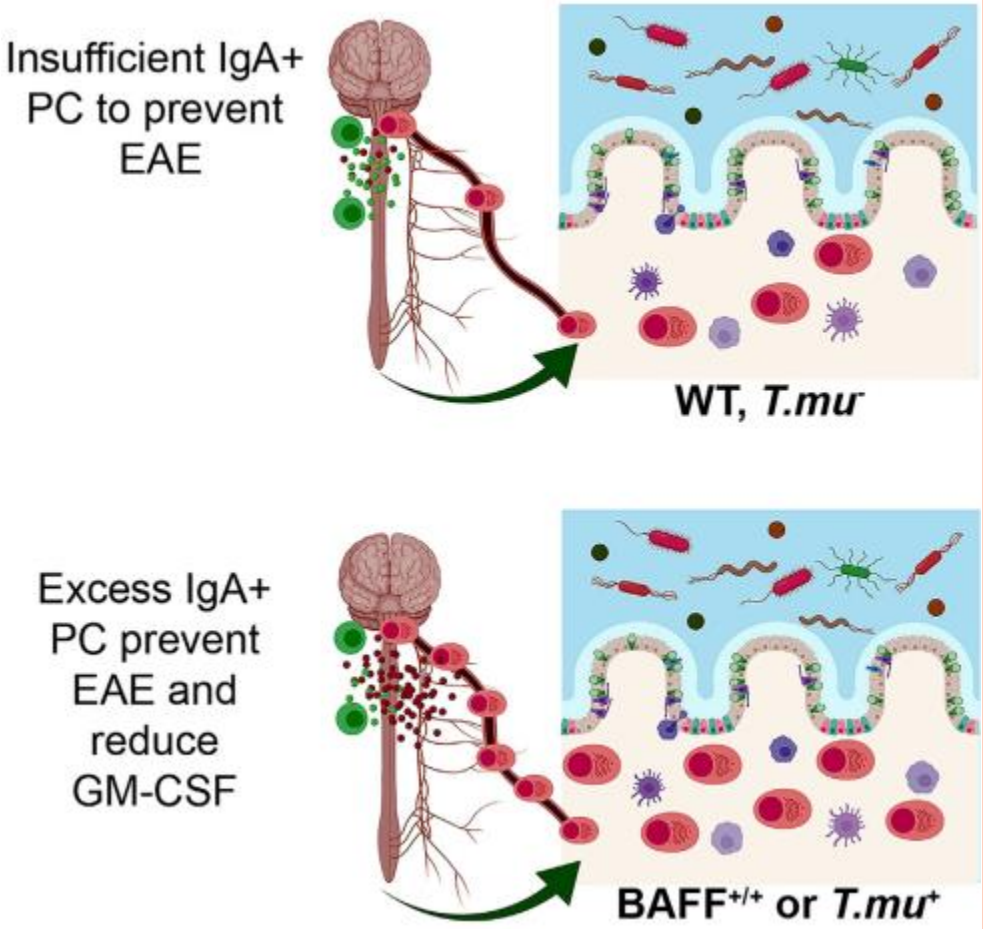
BIDIRECTIONAL TRAFFICKING OF DISTINCT B CELL CLONES

- Somatic hypermutation studies have demonstrated that, in individual patients, identical B cell clones can be shared between the CNS and the periphery thus suggesting bidirectional trafficking of distinct B cell clones
- Much of the clonal expansion of these B cells occurs in the deep cervical lymph nodes rather than in the CNS.
- The traditional view that the CNS is “immunologically privileged” is challenged
- Normal immunological surveillance can involve ongoing low-level immune cell trafficking across additional and molecularly distinct barriers (blood–leptomeningeal and blood–choroidal interfaces), and that the CNS also has a system of lymphatic egress that appears to involve drainage into deep cervical lymph nodes .
- Levels of the B cell and/or plasma cell chemo-attractants CXCL10, CXCL12 and CXCL13 are elevated in the CSF in people with MS
- CXCL13 levels have been suggested to predict an optimal response to B cell–depletion therapy (Alvarez *Mult. Scler. J. Exp. Transl. Clin* 2015

Cell

Recirculating Intestinal IgA-Producing Cells Regulate Neuroinflammation via IL-10

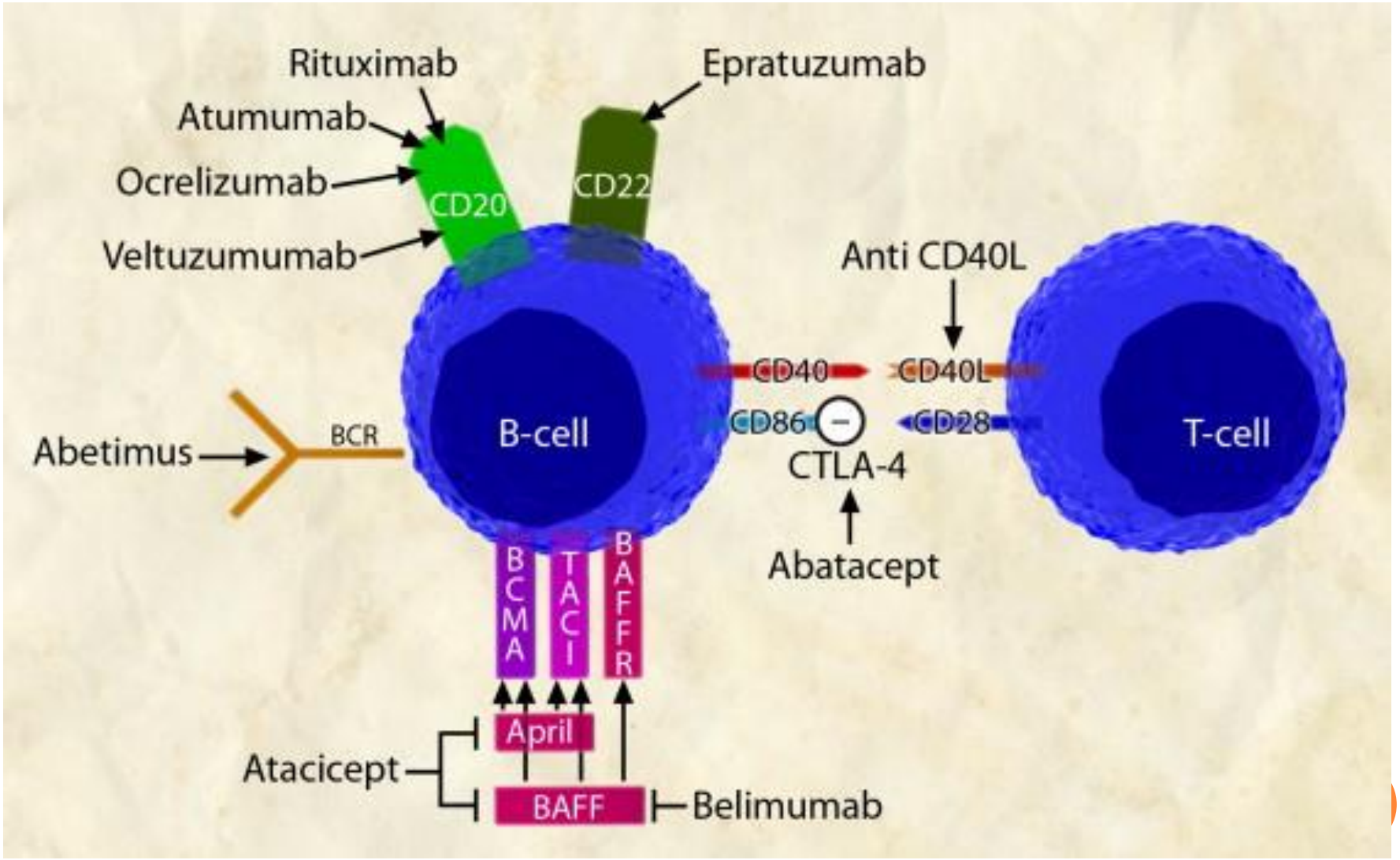
- Gut-derived IgA+ plasma cells (PC) access extra-intestinal tissues in the steady state
- Gut-derived IgA+ PC access the CNS during EAE and attenuate disease
- Removal of plasmablast (PB) plus PC resulted in exacerbated EAE that was normalized bythe introduction of gut-derived IgA+ PC.
  IgA+ PC attenuate EAE in an IL-10-dependent manner
- BAFF overexpression both confer resistance to EAE
- BAFF-Tg mice, which harbor IgA-producing cells in the CNS during the steady state, are highly resistant to both MOG35–55 and rhMOG-induced EAE, possibly due to TACI derived signals



Cell(2019),https://doi.org/10.1016/j.cell.2018.11.035

Failed B-cell therapy trials in MS

Anti B cell in MS therapeutics



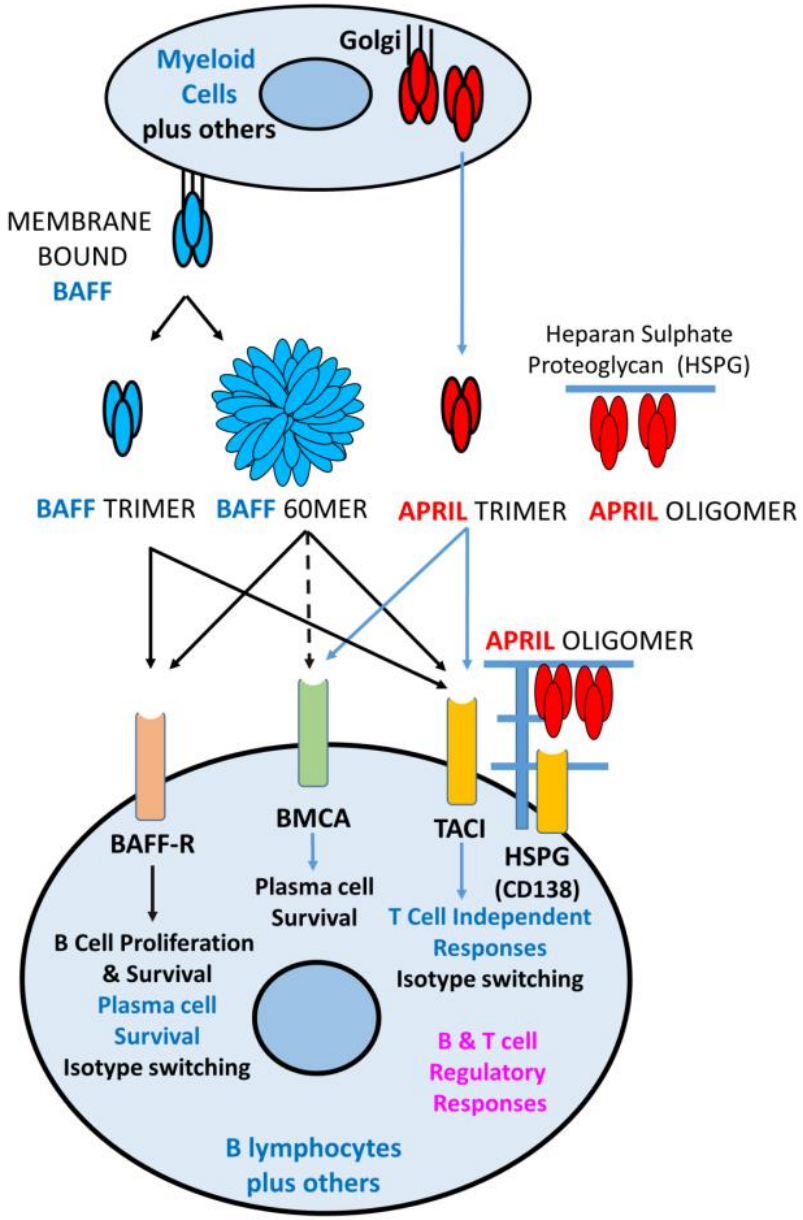
Atacicept in multiple sclerosis (ATAMS): a randomised, placebo-controlled, double-blind, phase 2 trial

*Ludwig Kappos, Hans-Peter Hartung, Mark S Freedman, Alexey Boyko, Ernst Wilhelm Radü, Daniel D Mikol, Marc Lamarine, Yann Hyvert, Ulrich Freudensprung, Thomas Plitz, Johan van Beek, for the ATAMS Study Group**

- **90 (35%) patients completed the week 36 treatment visit, 26 (10%) discontinued before study termination and 139 (55%) discontinued because of study termination.**
- **During the double-blind period of ATAMS, ARRs were higher in the atacicept groups than in the placebo group (atacicept 25 mg, 0·86, 95% CI 0·43–1·74; 75 mg, 0·79, 0·40–1·58; 150 mg, 0·98, 0·52–1·81; placebo, 0·38, 0·17–0·87).**
- **Mean numbers of gadolinium-enhancing T1 lesions per scan were similar in all groups (25 mg, 2·26, 0·97–5·27; 75 mg, 2·30, 1·08–4·92; 150 mg, 2·49, 1·18–5·27; placebo, 3·07, 1·40–6·77)**

***Lancet Neurol* 2014; 13: 353–63**

BAFF, APRIL TACI



❖Tabalumab is a human IgG4 monoclonal antibody that neutralizes membrane and soluble BAFF[NCT008829999].

❖Belimumab is a human IgG1 monoclonal antibody,licenced for the treatment of systemic lupus erythematosus, which targets soluble BAFF, notably the trimeric BAFF molecule

❖ Atacicept is a fusion protein of TACI and constant regions of human IgG1 that blocks BAFF and APRIL

❖Both tabalumab and atacicept induce depletion of mature B cells and inhibit antibody-formation, but they fail to deplete memory B cells and do not inhibit relapsing MS

SILENT PROGRESSION IS INDEPENDENT OF RELAPSES

- Relapses were associated with a transient increase in disability over 1-year intervals (p = 0.012) but not with confirmed disability progression (p = 0.551)
- Long-term worsening is common in relapsing MS patients, is largely independent of relapse activity, and is associated with accelerated brain atrophy.

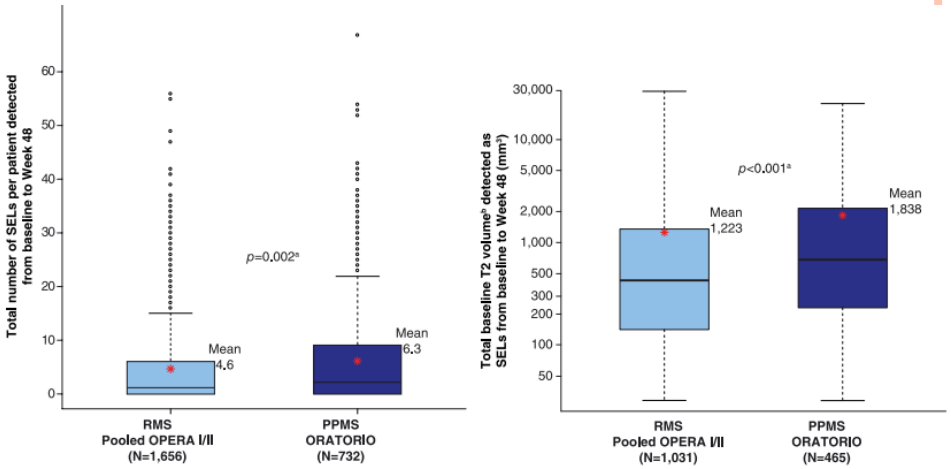
- Baseline innate immune cell activation in the normal-appearing white matter was a significant predictor of later progression when the entire multiple sclerosis cohort was assessed [odds ratio (OR) = 4.26; P = 0.048].
- In the patient subgroup free of relapses there was an association between macrophage/microglia activation in the perilesional normal-appearing white matter and disease progression (OR = 4.57; P = 0.013).
- None of the conventional MRI parameters measured at baseline associated with later progression.

ANN NEUROL 2019;85:653–666

*Brain 2020;*143(11):3318–3330

Slowly expanding lesions as an MRI marker of chronic active MS lesions

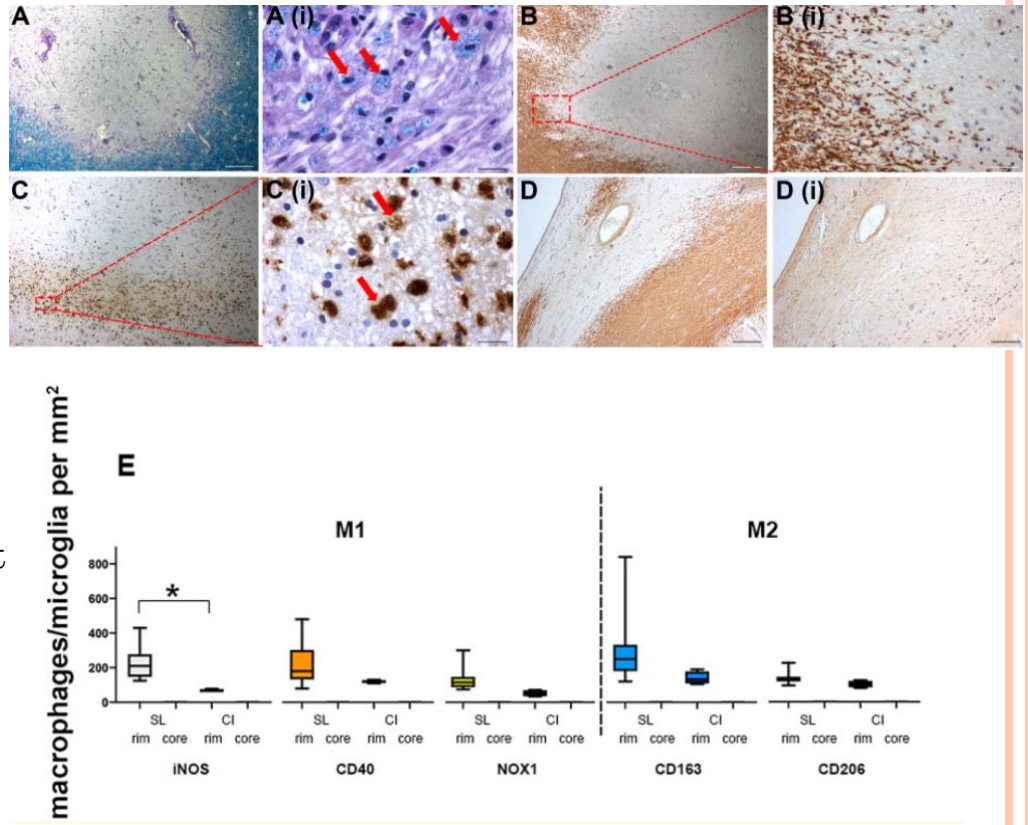
- Compared with RMS patients, PPMS patients had higher numbers of SELs (p=0.002) and higher T2 volumes of SELs (p<0.001). SELs were devoid of gadolinium enhancement.
- Compared with areas of T2 lesions not classified as SEL, SELs had significantly lower T1 intensity at baseline and larger decrease in T1 intensity over time.
- **Conclusion:**
  - We suggest that SELs reflect chronic tissue loss in the absence of ongoing acute inflammation.
  - SELs may represent a conventional brain MRI correlate of chronic active MS lesions and a candidate biomarker for smoldering inflammation in MS



MSJ 2019, Vol. 25(14) 1915–1925

SLOWLY EXPANDING LESIONS &PROGRESSIVE MS

- By applying the microglia-specific marker TMEM119, we demonstrate that cells accumulating at the lesion edge almost exclusively belonged to the microglia lineage..
- … we observed a preferential accumulation of M1-type differentiated cells at the lesion edge, indicating a crucial role of these cells in lesion progression.
- In slowly expanding lesions, we identified a total of 165 genes that were upregulated and 35 genes that were downregulated. The upregulated genes included macrophage/microglia-associated genes involved in immune defence and inflammatory processes. Among the upregulated genes were ALOX15B, MME and TNFRSF25

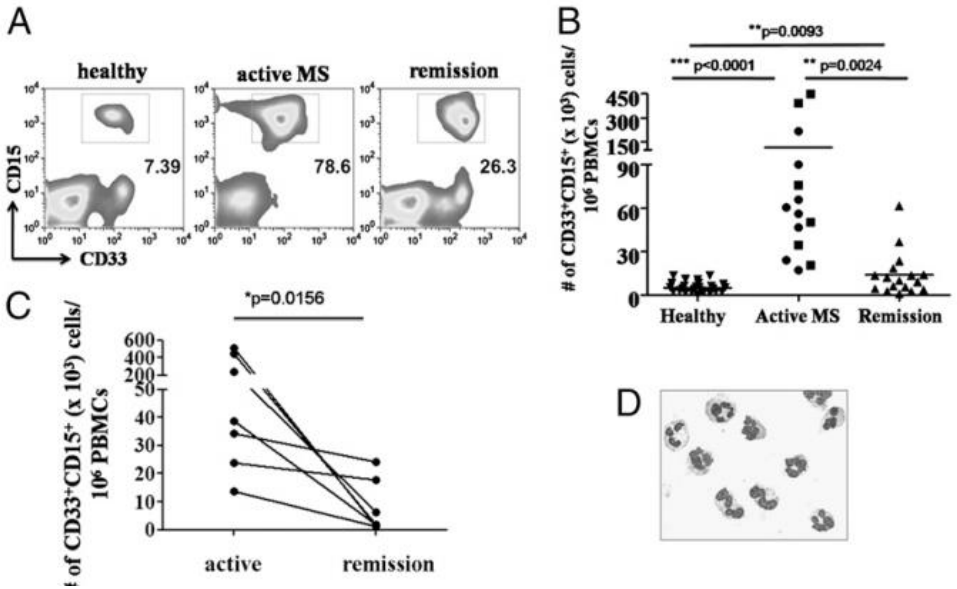


BRAIN 2020: 143; 2073–2088

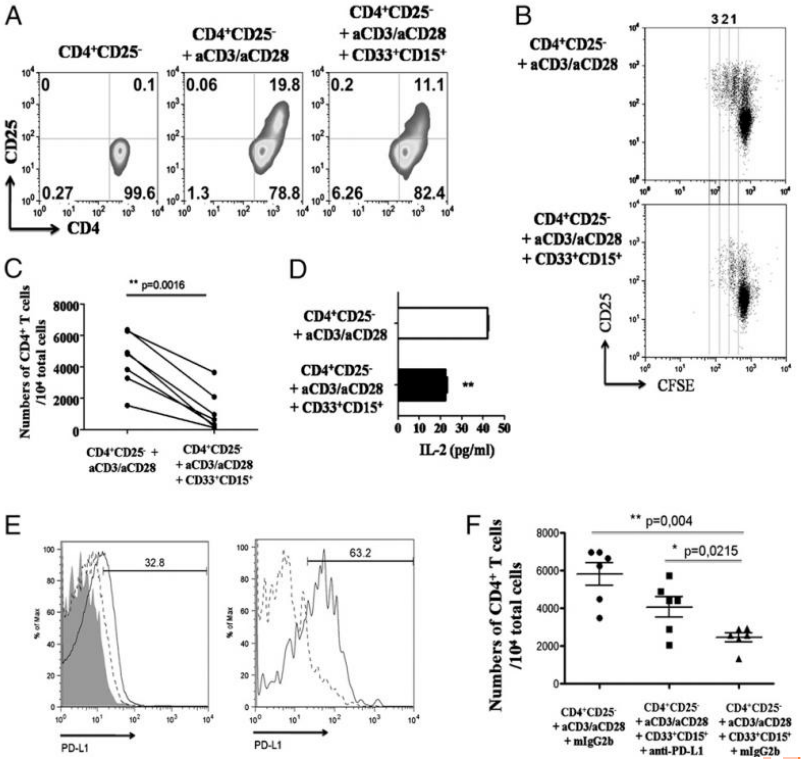
Crucial Role of Granulocytic Myeloid-Derived Suppressor Cells in the Regulation of Central Nervous System Autoimmune Disease

doi:10.4049/jimmunol.1101816

Marianna Ioannou,*,† Themis Alissafi,*,† Iakovos Lazaridis,‡ George Deraos,§ John Matsoukas,§ Achille Gravanis,‡ Vasileios Mastorodemos,¶ Andreas Plaitakis,¶ Arlene Sharpe,‖ Dimitrios Boumpas,*,† and Panayotis Verginis*,†



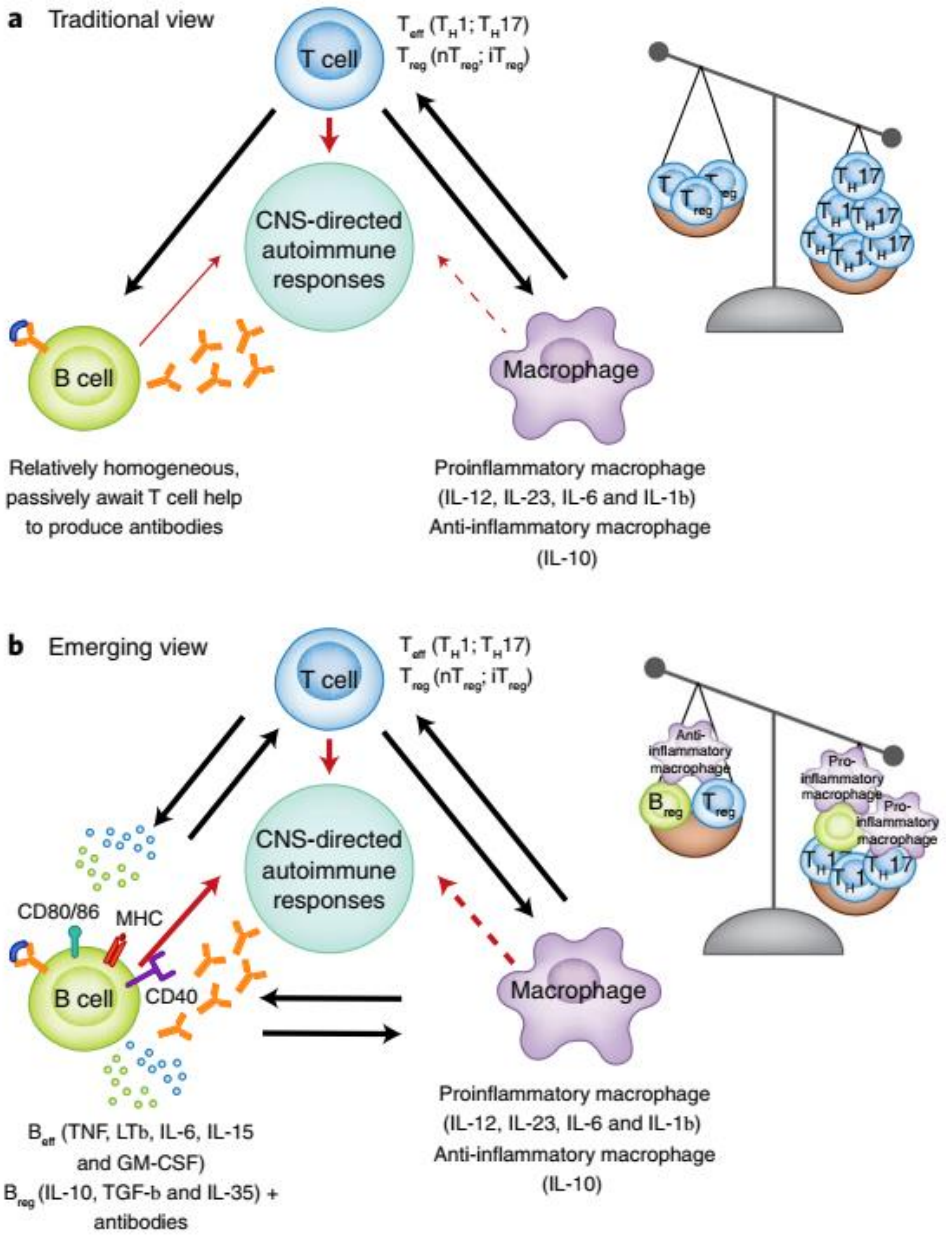
G-MDSCs are enriched in the periphery of active MS patients



CD33+CD15+ MDSCs from active MS patients potently suppress the proliferation of autologous T cells in vitro

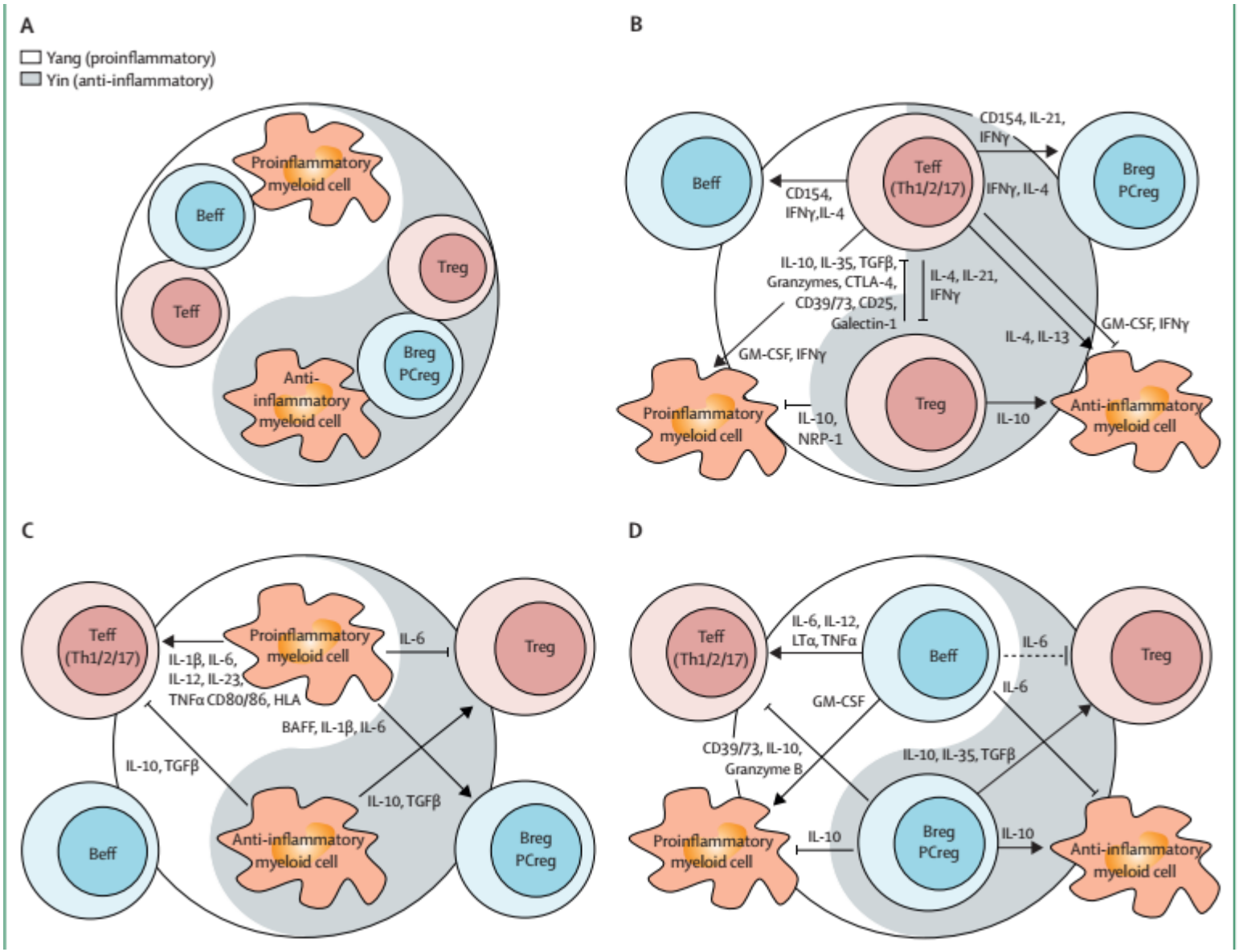
An evolving view of cell-subset contributions to MS pathophysiology

The updated view. Results of aCD20 therapy in MS highlight a more central role of B cells in new MS attacks, which appears not to be antibody dependent. Antibody-independent roles of B cells, in part mediated through elaboration of distinct cytokines, can manifest as either proinflammatory effector B cells (Beff) or anti-inflammatory regulatory B cells (Breg). These cells can activate (Beff) or downregulate (Breg) proinflammatory responses of both T cells and myeloid cells. Bidirectional interactions among functionally distinct B cells, T cells and myeloid cells, and the consequences of such interactions, underlie the development of new MS attacks.



Nature immunology 2018

THE YIN AND YANG OF CELLULAR IMMUNOLOGY IN MULTIPLE SCLEROSIS



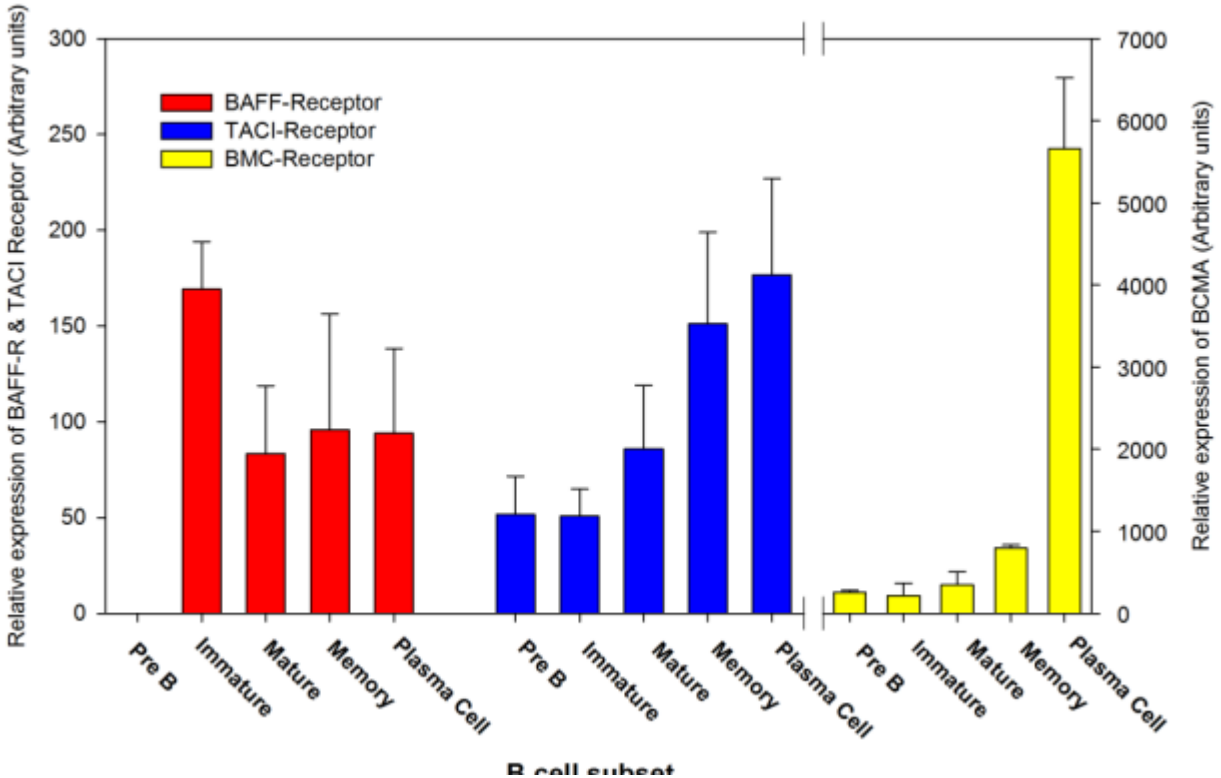
Lancet Neurol 2021; 20: 470–83

Σας ευχαριστώ

BIDIRECTIONAL TRAFFICKING OF DISTINCT B CELL

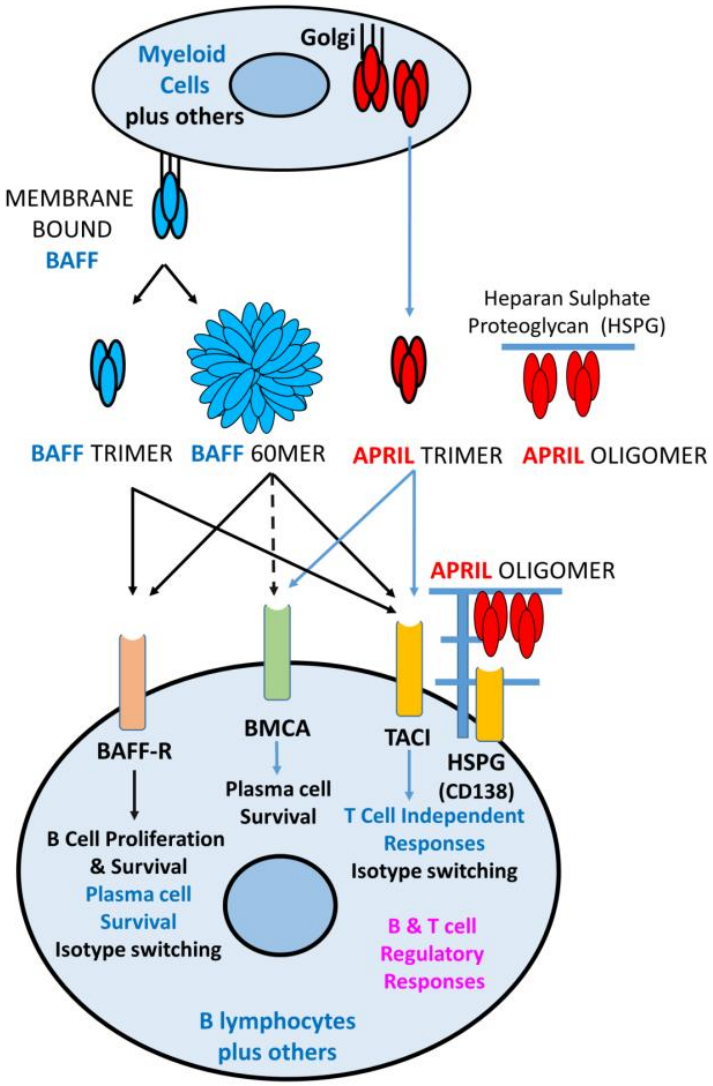
- bidirectional trafficking of distinct B cell clones (both into and out of the CNS) and in fact suggest that much of the clonal expansion of these B cells occurs in the deep cervical lymph nodes rather than in the CNS
- Levels of the B cell and/or plasma cell chemo-attractants CXCL10, CXCL12 and CXCL13 are elevated in the CSF in people with MS
- CXCL13 levels have been suggested to predict an optimal response to B cell–depletion therapy (Alvarez *Mult. Scler. J. Exp. Transl. Clin* 2015)

Gene expression of B cell growth factor receptors by B cell subsets



❖Atacicept is reported to augment memory B cell responses and may precipitate relapse suggesting the importance of APRIL

BAFF, APRIL, TACI



- B cell activating factor (BAFF/Tumour necrosis factor superfamily member 13B (TNFS13B/CD257)) promotes maturation and survival of B cells and is the dominant homeostatic regulator of peripheral B cell pools.
- This binds and acts via the transmembrane activator, calcium modulator and cyclophilin ligand interactor (TACI/TNFSR13C/CD267) receptor, the BAFF-receptor (BAFF-R/TNFSR13B/CD268) and the B cell maturation antigen (BCMA/TNFSR17/CD269)
- However, BAFF binds to the BAFF-R with significantly higher affinity than BCMA . This latter receptor is also bound by a proliferation-inducing ligand (APRIL/ TNFSF13/CD256). APRIL acts on TACI, BCMA but, not BAFF-R and binds to BMCA with a higher affinity than BAFF

Introduction

Immunological tolerance refers to the **specific immunological non-reactivity** (unresponsiveness) to an antigen due to a previous exposure to the same antigen.

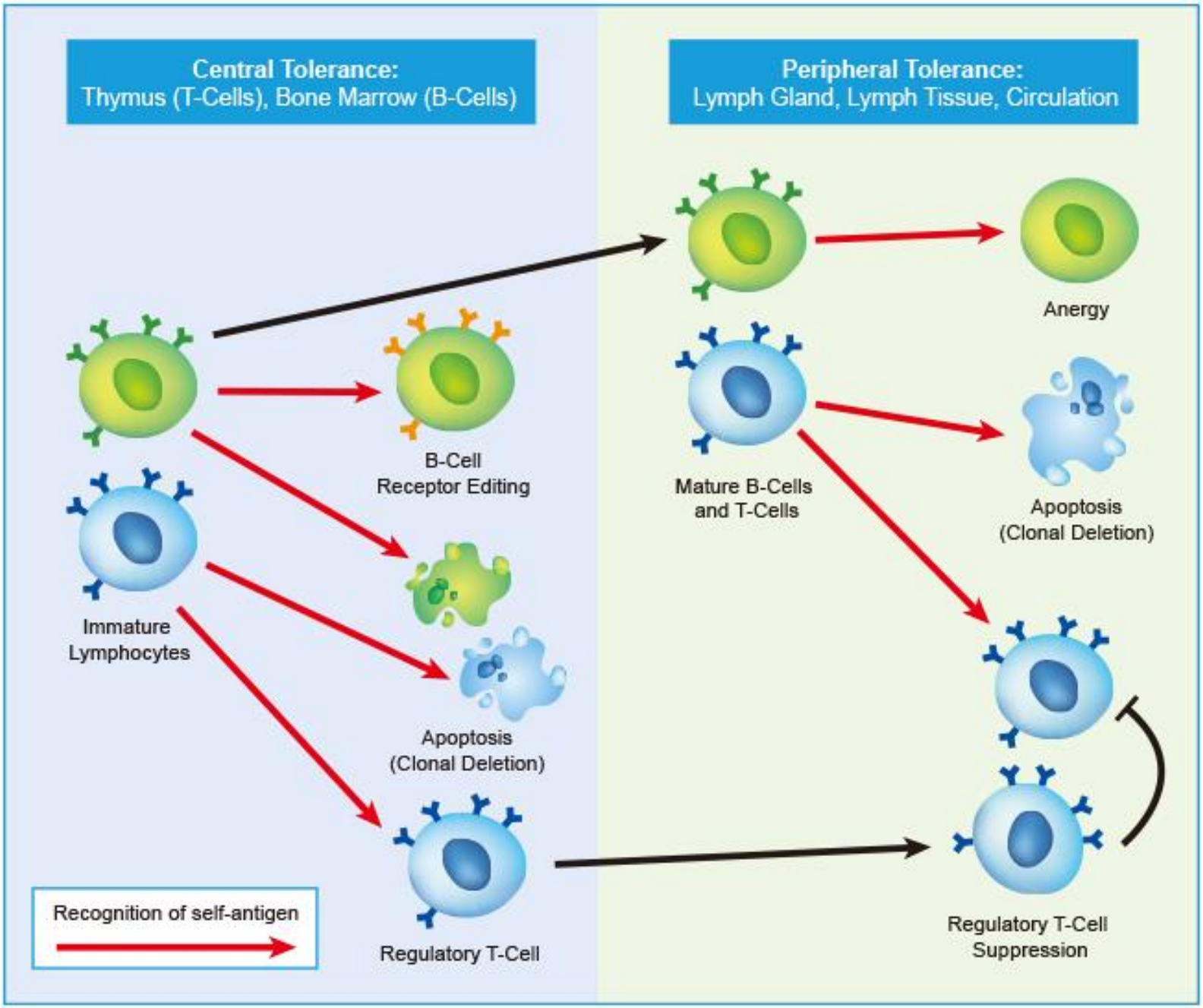
While the most important form of tolerance is non-reactivity to self antigens, it is possible to induce tolerance to non-self antigens. When an antigen induces tolerance, it is termed as **Tolerogens**.

Tolerance is different from non-specific immunosuppression and immunodeficiency. It is an **active antigen-dependent** process in response to the antigen.

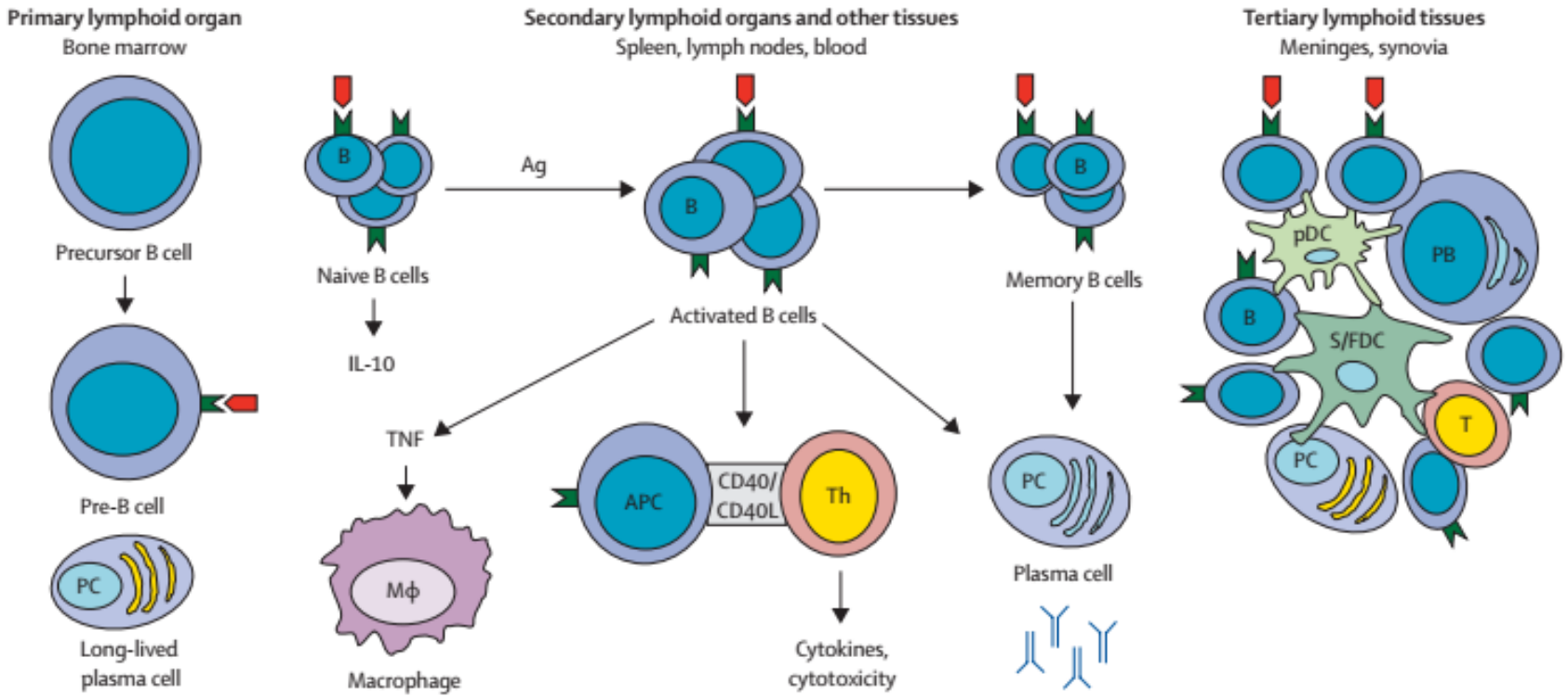
- Two major checkpoints contribute to normal elimination and control of autoreactive B cells: central tolerance and peripheral tolerance.

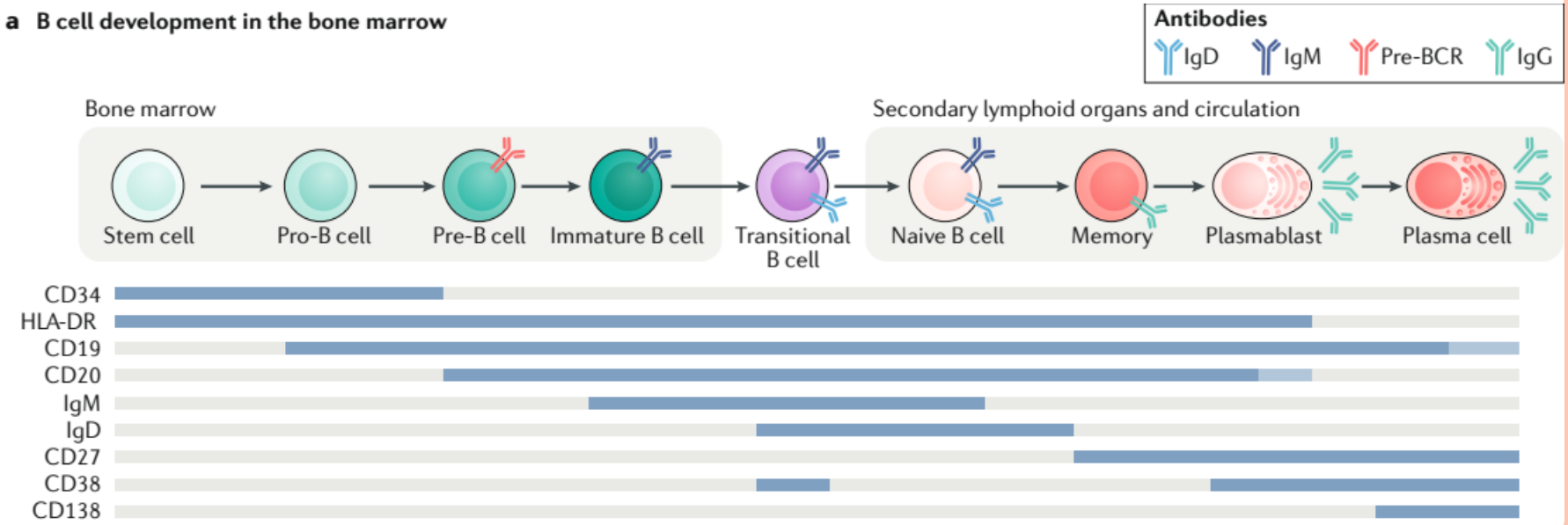
- Central B cell tolerance is established in the bone marrow and involves the elimination of approximately 75% of self-reactive B cells. B cell receptor– and Toll-like receptor (TLR)-signaling pathways play important roles during the selection of B cells in the bone marrow .

- Peripheral tolerance takes place in the secondary lymphoid organs, where most other self-reactive B cells are controlled. CD40–CD40L receptor–ligand pair, the major histocompatibility complex (MHC) and Treg cells are considered important for control of autoreactive B cells in the periphery.


Central Tolerance:
Thymus (T-Cells), Bone Marrow (B-Cells)
Peripheral Tolerance:
Lymph Gland, Lymph Tissue, Circulation
Anergy
B-Cell
Receptor Editing
Mature B-Cells
and T-Cells
Apoptosis
(Clonal Deletion)
Immature
Lymphocytes
Apoptosis
(Clonal Deletion)
Recognition of self-antigen
Regulatory T-Cell
Regulatory T-Cell
Suppression

B-CELL LINEAGES IN DIFFERENT BODY COMPARTMENTS





B cell receptor (BCR). A cell-surface immunoglobulin composed of two paired heavy (H) and light (L) chains. Each chain is generated by irreversible rearrangement and recombination of the B cell variable (V), diversity (D; heavy chain only) and junction (J) genes

Immunoglobulin class switching ='isotype class switching' or 'class-switch recombination', this process refers to recombination of the immunoglobulin gene constant (C) region to allow generation of IgG, IgA or IgE isotypes.

Germinal centre reaction
The formation of secondary lymphoid tissue, which is the site of B cell somatic hypermutation and isotype switching

- B cells originate from stem cells in the bone marrow and undergo B cell receptor (BCR) rearrangement and upregulation of CD34 and HLA-DR cell-surface proteins.

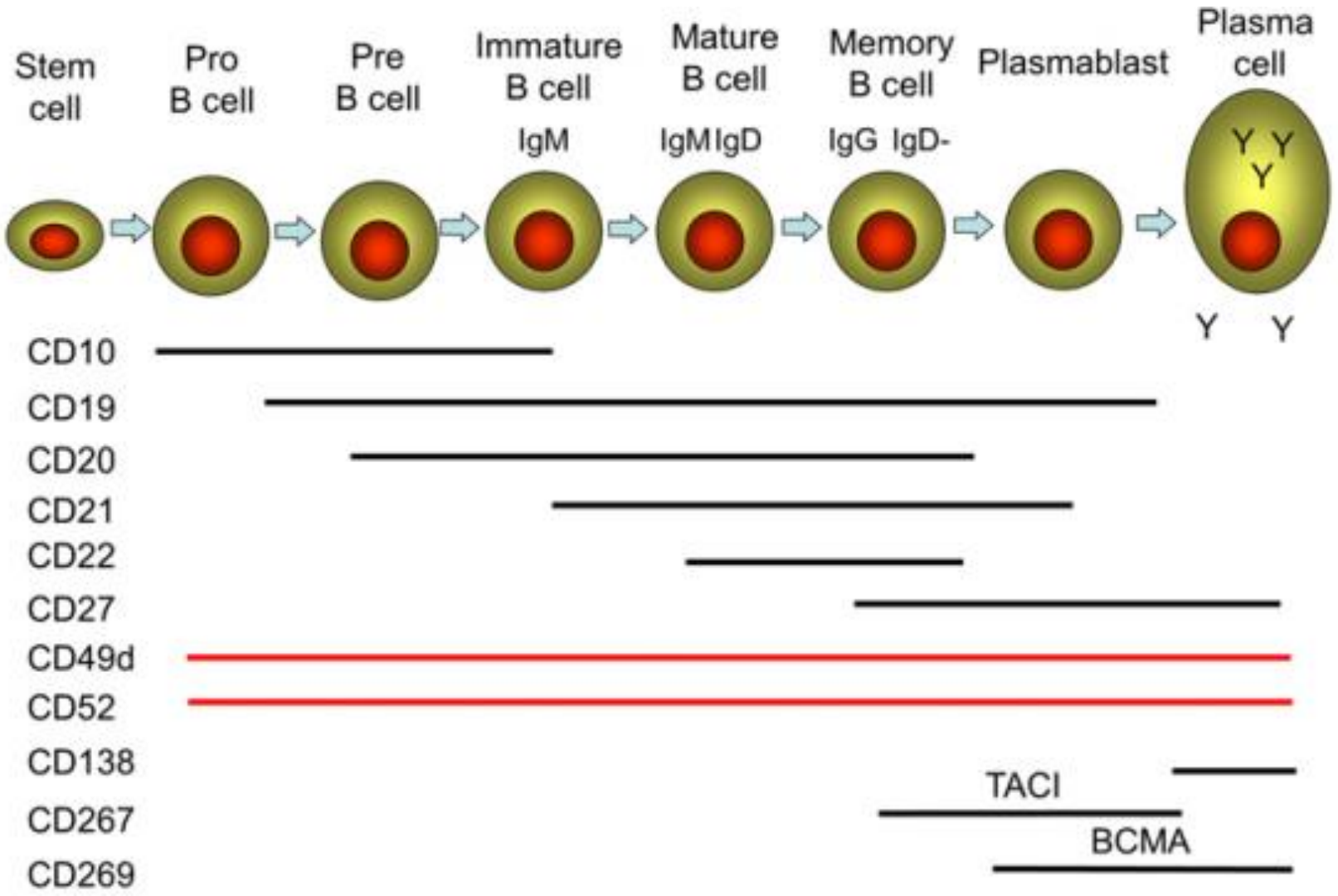
- Pre-B cells express a BCR consisting of a rearranged heavy chain and a surrogate invariant light chain (pre-BCR).

- Immature B cells begin to express IgM and exit the bone marrow, becoming transitional B cells, which express IgM with or without IgD.

- Naive B cells co-express IgM and IgD, and can either remain in the circulation or migrate to secondary lymphoid organs.

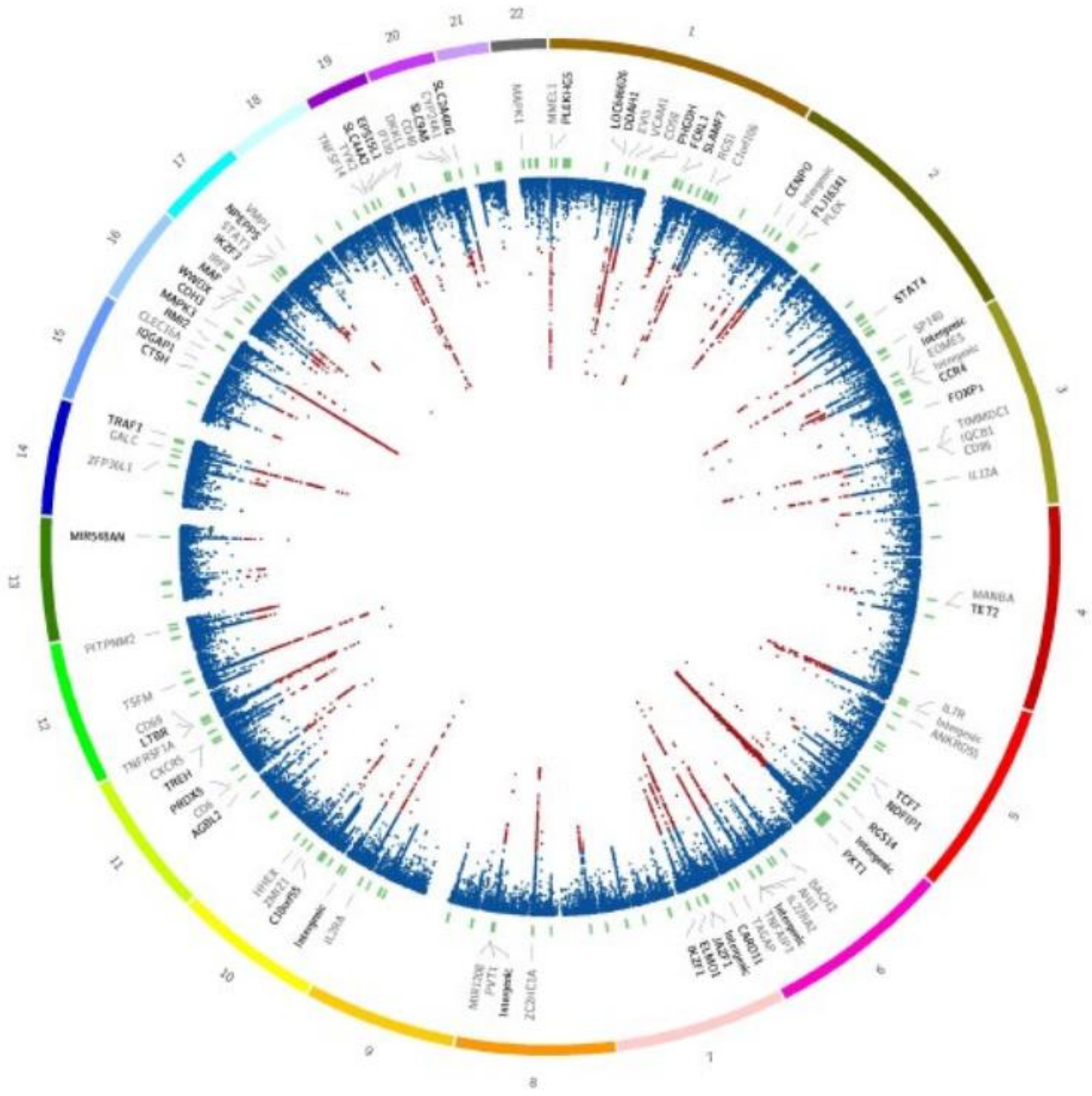
- Each differentiation stage is associated with specific changes in protein expression. Although class switched memory B cells are typically CD27+IgD– B cells, other memory B cell subtypes can be generated (including outside germinal centres), such as CD27+IgD+ B cells (unswitched memory cells) and CD27–IgD– B cells (double-negative B cells)

B CELL LINEAGE AND SURFACE MARKER EXPRESSION



TACI =(transmembrane activator and CAML interactor) protein and
BCMA =(B cell maturation antigen).

Immunochip MS



- 14498 MS cases and 24091 controls of european anscestry
- 161 311 SNP markers
- 135 associated regions
- 48 novel loci replicated
- Total number non-HLA associations 110

IMSGC Nature Genetics 2013 45(11):1353-60

Genetic regions associated with MS

Karolinska Institutet