Ο ρολος των Τ cells στο Νευρολογικο νοσημα

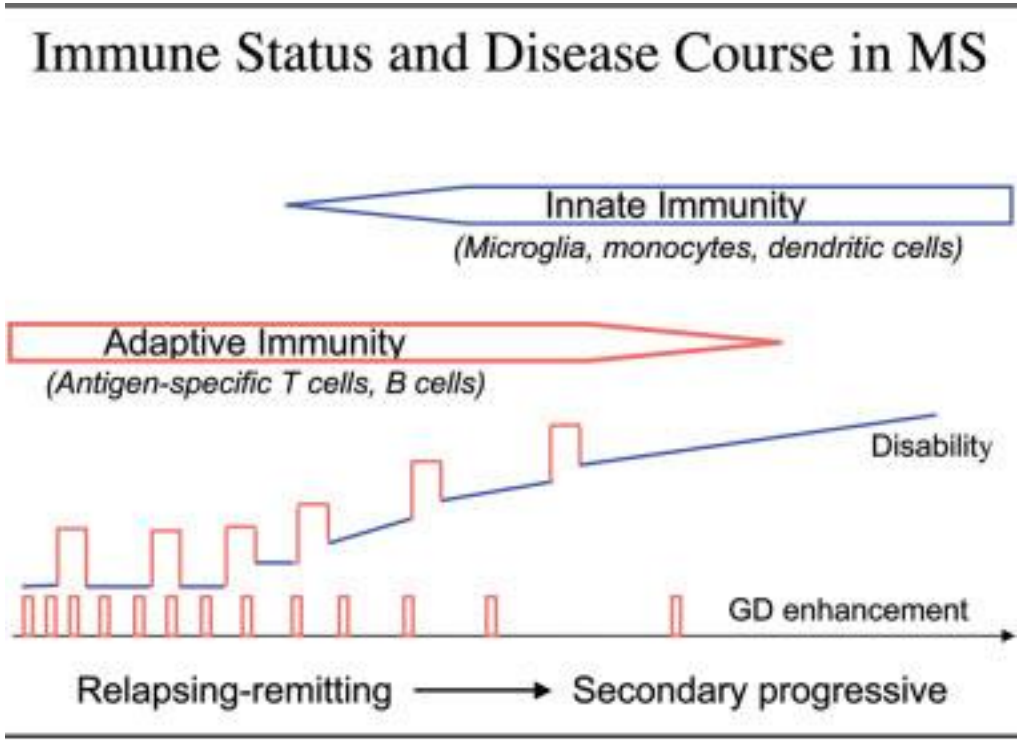
Κ ΚΥΛΙΝΤΗΡΕΑΣ

Καθηγ Νευρολογιας

T-cell [ms,autoimmune encephalitis intracellular antigens, Polymyositis ,

B-cells[NMO,MS-type II neuropathology ,anti-MOG related syndromes,paraproteinemic neuropathies, antigagglioside neuropathies ,autoimmune encephalopathies-extracellular antigens myasthenia gravis dermatomyositis]

Disease course and Immunity



T-cell activation

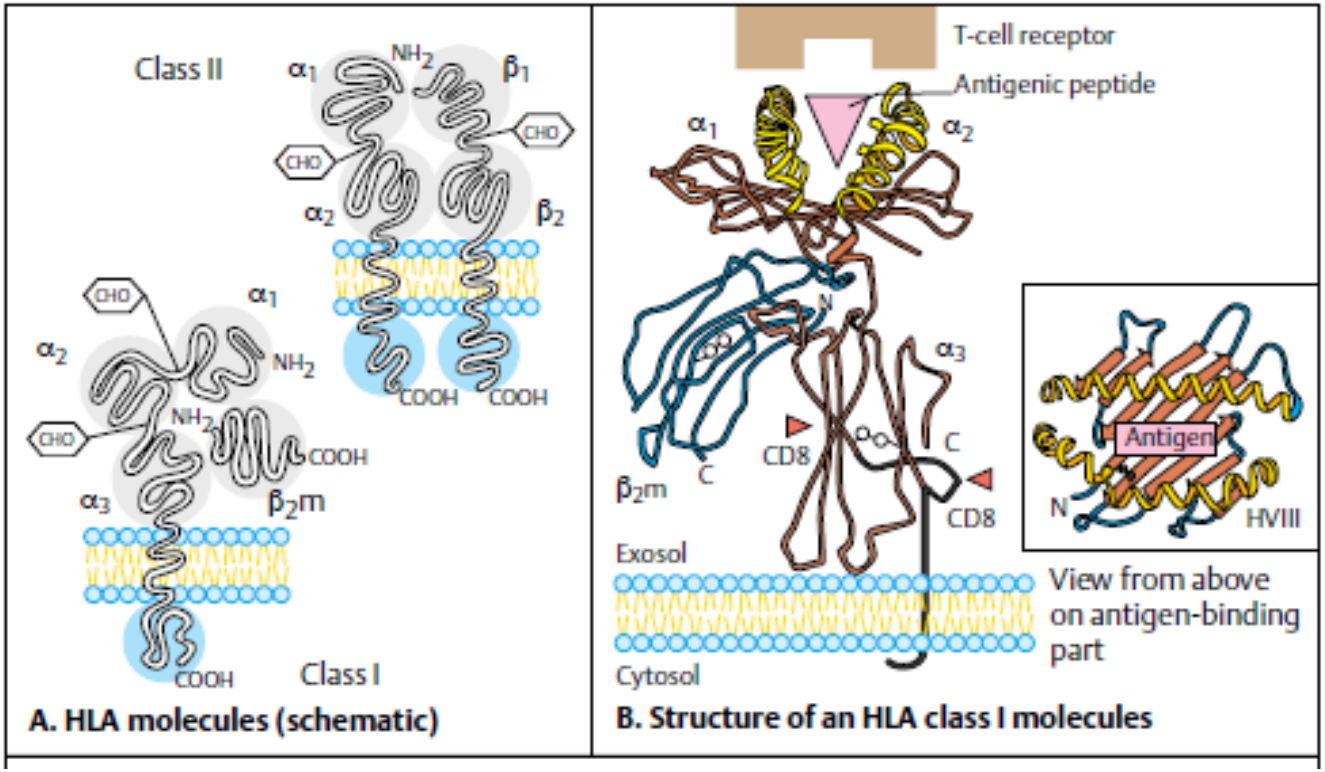
- Trimolecular complex
- Acessory molecules
- CD28 and B7
- CTLA-4 and B7
- CD2

Peripheral activation of T-cell

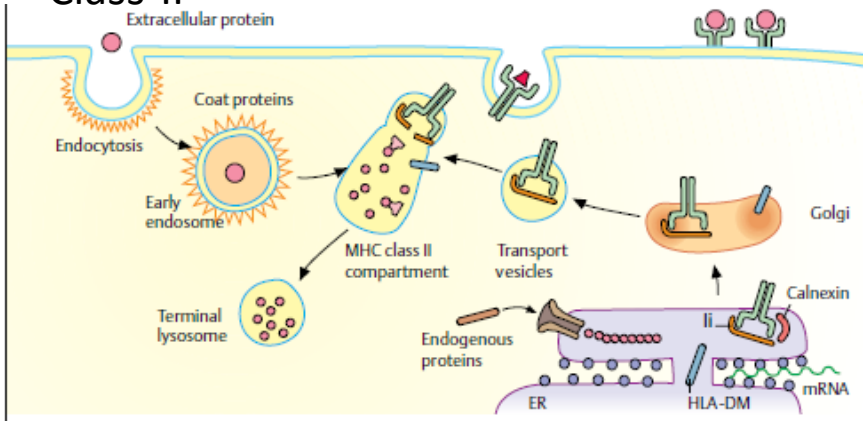
- CNS antigen fragments in circulation or in lymph drainage
- Molecular mimicry
- Subpopulation of MBP reactive cells respond to EBV,Herpes simplex ,innfluenza virus antigen fragments
- Superantigens

Trimolecular complex
MHC-II - Ag - TCR

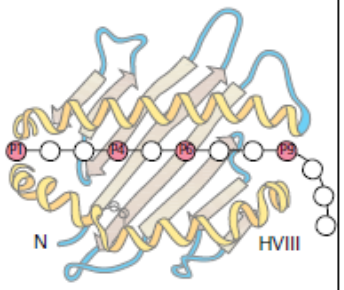
- MHC-I , MH-II [antigen recognition]
- MHC-III [Complement]
- Consist of
- Polymorfism
- Determinant selection
- Immunoglobulin gene superfamily


Class II
α1
NH2
β1
CHO
CHO
α2
β2
COOH
COOH
CHO
α1
α2
NH2
NH2
CHO
COOH
α3
β2m
COOH
Class I
A. HLA molecules (schematic)
T-cell receptor
Antigenic peptide
α1
α2
N
α3
CD8
C
C
β2m
CD8
Exosol
Cytosol
Antigen
N
HVIII
View from above on antigen-binding part
B. Structure of an HLA class I molecules

Class-II



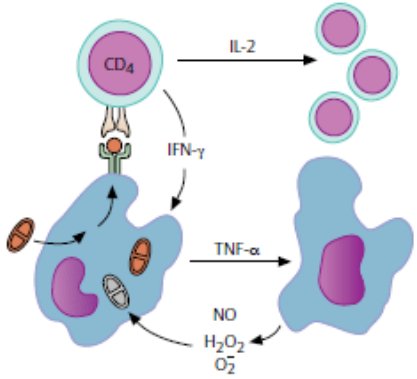
A. MHC class II-dependant antigen processing

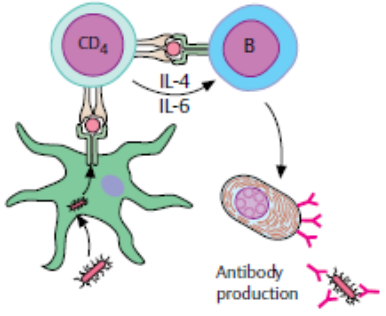


B. Anchor AA in MHC II peptides

	Anchor AA	Inhibitory AA
P1	Phe, Ile, Leu, Met, Val, Trp, Tyr	
P4	Asp, Met, Gln, Ser	Gly, Lys, Pro, Arg, Trp, Tyr
P6	Ser, Thr, Val	Gln, Phe, Gly, His, Lys, Leu, Met, Tyr
P9	Ser	Asp, Gln, Leu, Asn, Pro

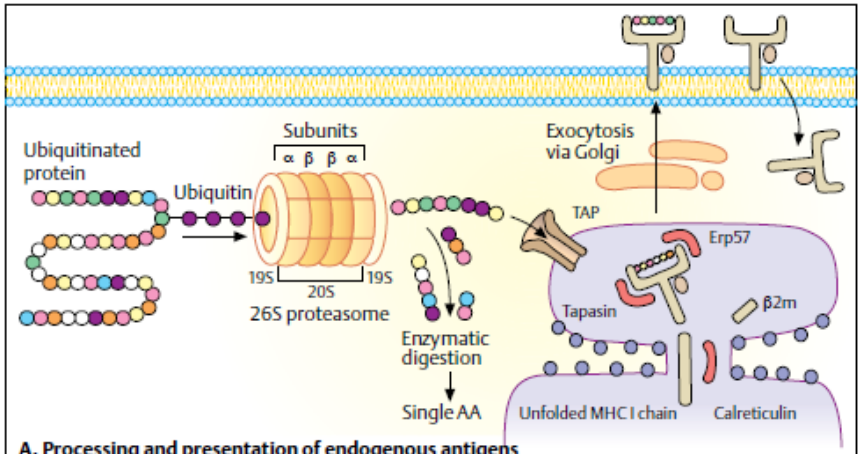
C. Allele-specific motifs in DRB1*0401-binding peptides



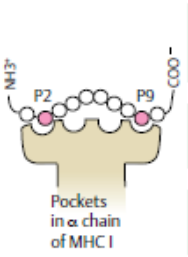


D. T-cell activation via MHC II

CLASS-I



A. Processing and presentation of endogenous antigens

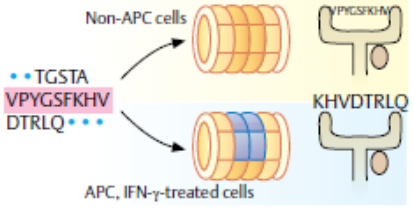


HLA-A*0201	P2=Leucine P9=Valine, Tyrosine
HLA-A3:	P2=Leucine P9=Lysine
HLA-B7:	P2=Leucine P9=Proline

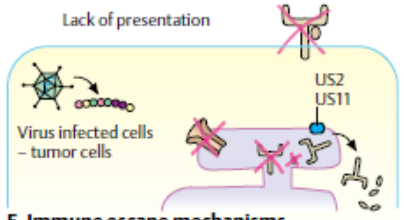
B. Binding motifs

MAPPQVLAFGLLLAAATATFAAAQEECVLENY
KLAVNCFVNNNRQCQCTSVGAQNTVICSKL
AAKCLVMKAEMNGSKLGRRAKPEGALQNND
GLYDPDCDESGLFKAKQCNGTSTCWCVNTA
GVRRTDKDTEITCSERVRTYWIIIELKHKAREK
PYDSKSLRTALQKEITTRYGLDPKFITSILYENN
VITIDLVQNSQQKTQNDVDIADVAYYVEKDV
KGESLFSHKKMDLTVNGEQLDLDPGQTLIYY
VDEKAPEFSMQGLKAGVIAVIVVVVIAVVAGI
VVLVISRKKRMAKIEKAEIKEMGEMHRELNA

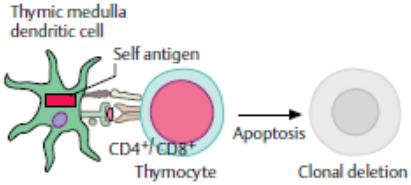
C. HLA-A2-binding epitopes of a 314 AA protein



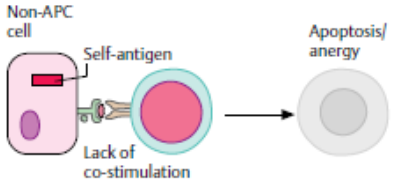
D. Immunoproteasome



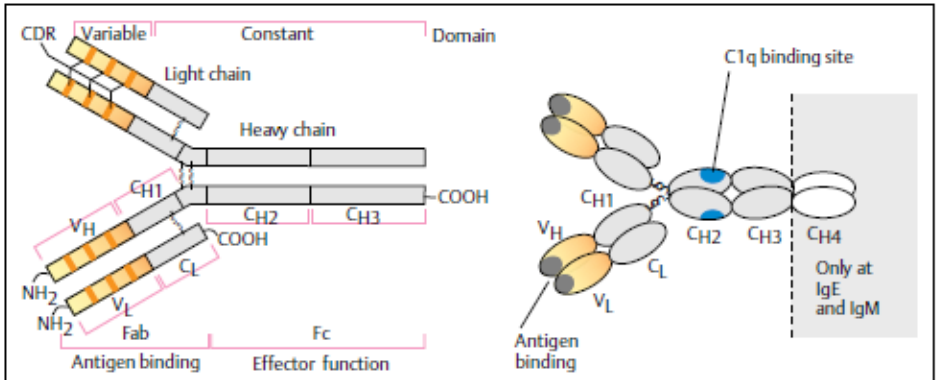
E. Immune escape mechanisms



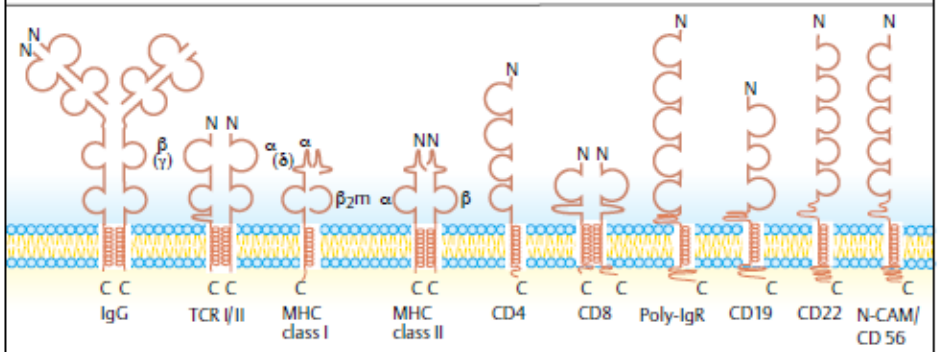
F. Central tolerance to self antigens



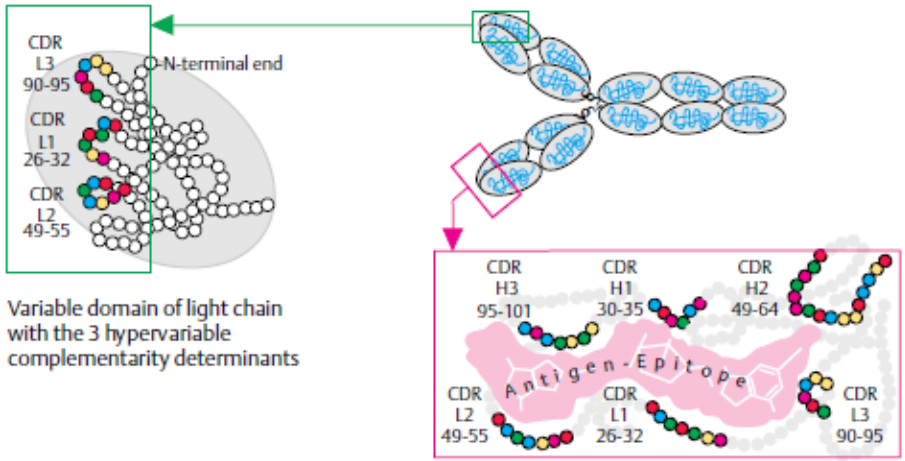
G. Peripheral tolerance to self-antigens



A. Immunoglobulin structure



B. Immunglobulin-"superfamily"



C. Hypervariable regions determine the antigen specificity

TABLE 21.6 Some HLA Disease Associations

Disease	MHC-I	Strength of Association
Ankylosing spondylitis	HLA-B27	+++
Reiter disease	HLA-B27	++
Psoriasis	HLA-C*06	+
Abacavir drug hypersensitivity	HLA-B*57:01	+++
Behcet disease	HLA-B*51	+
Birdshot retinopathy	HLA-A*29	+++
Insulin-dependent diabetes mellitus	HLA-DQ8	++
	HLA-DQ2	+
	HLA-DR2	-
Rheumatoid arthritis	HLA-DR4	+
Celiac disease	HLA-DQ2	+++
	HLA-DQ8	+
Multiple sclerosis	HLA-DR2	+

HLA, human leukocyte antigen; MHC, major histocompatibility complex

+++ = very strong association that is clinically useful as a diagnostic tool

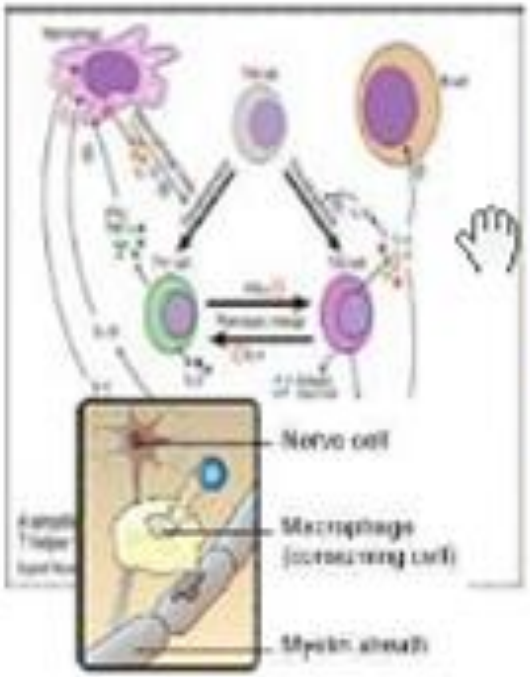
++ = strong association with likely primary involvement in disease pathogenesis

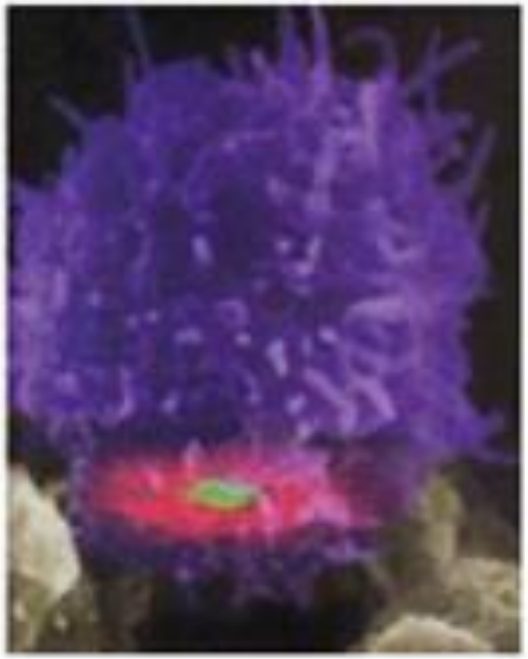
+ = clear association with likely role in disease pathogenesis

- = negative or protective influence on disease probability

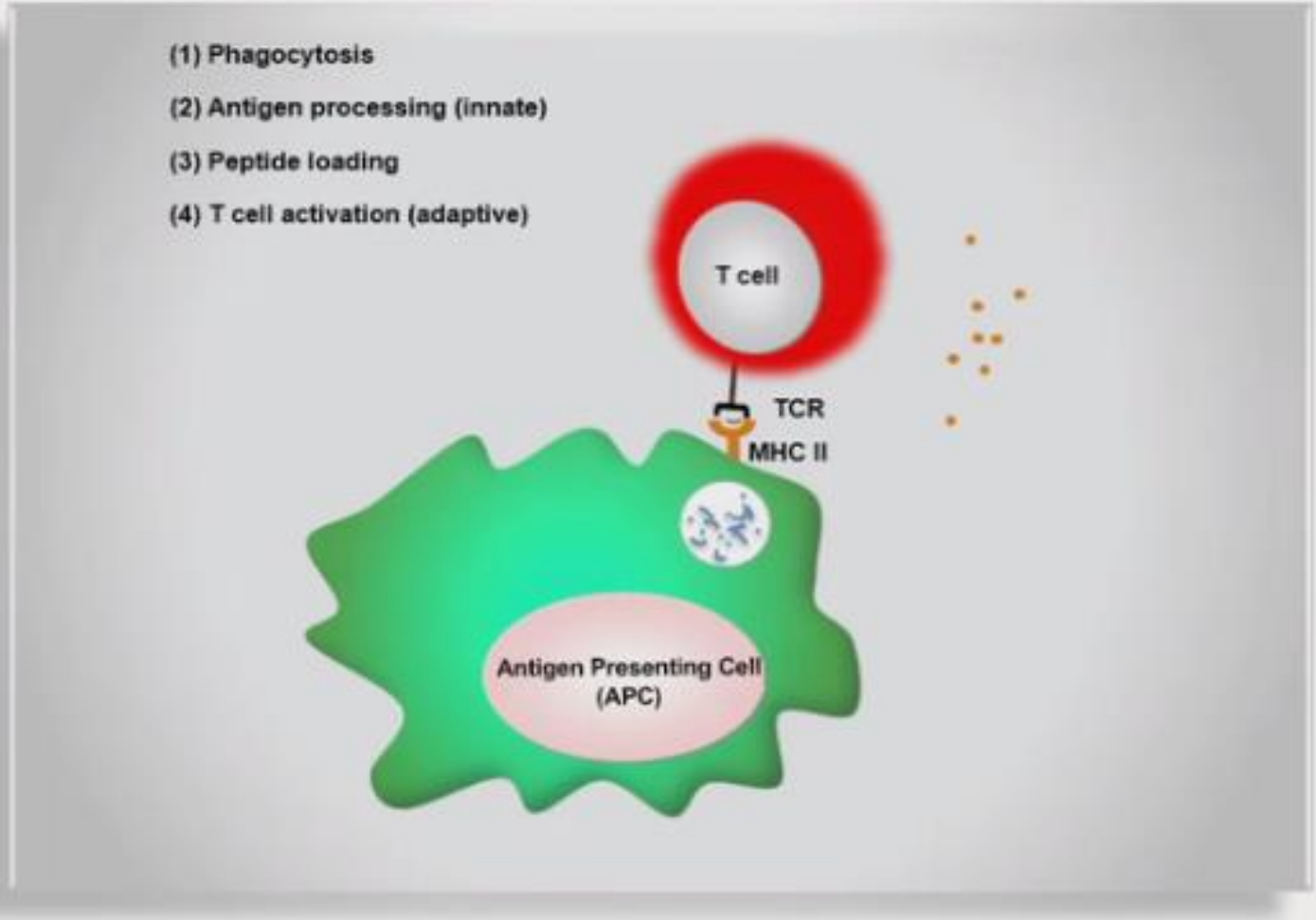
For a more detailed summary of MHC and disease associations see Shiina et al.220

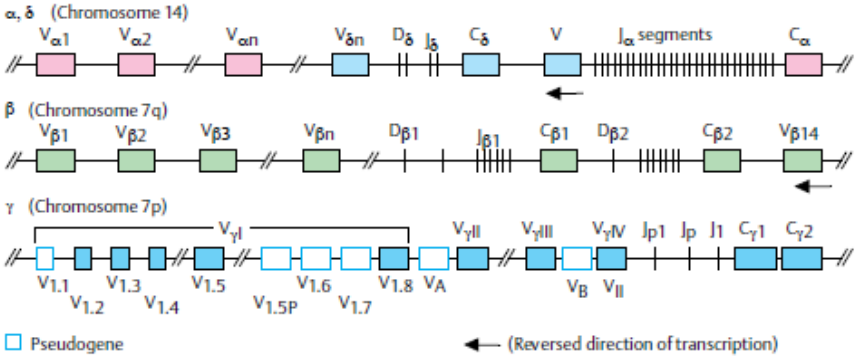
Trimolecular complex in person



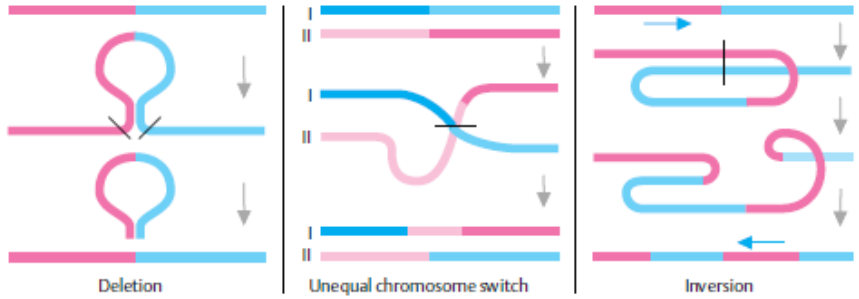


MHC class II-restricted antigen presentation
(connects innate and adaptive immunity)

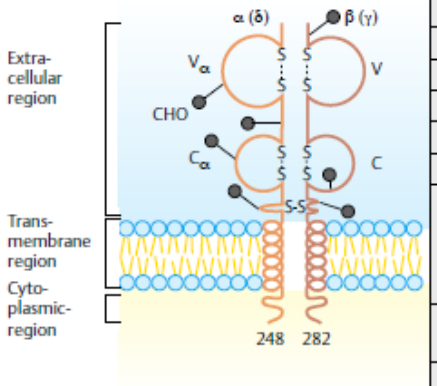




A. T-cell receptor gene families



B. T-cell receptor rearrangement



α chain = V - J - C
β chain = V - D - J - C
δ chain = V - D - J - C
γ chain = V - J - C

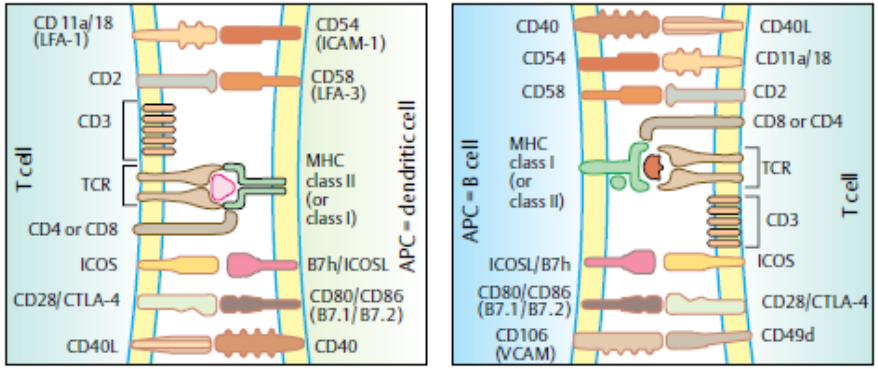
C. Configuration of the T-cell receptor

Gene segments	α-chain	β-chain
V	100	100
D	0	2
J	100	13
V x D x J-combinations	10^4	2×10^3
N-sequences	10^4	10^4
Total number of α/β combinations		10^{15}

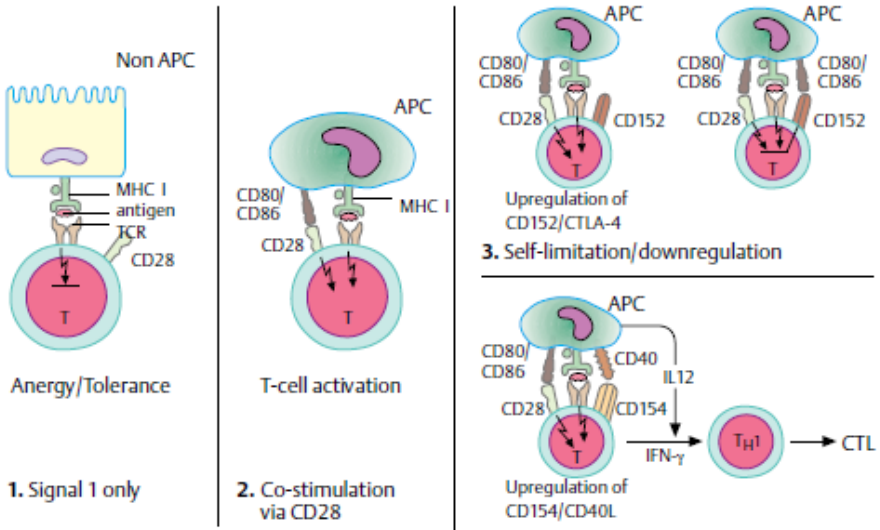
D. Possible combinations of the T-cell receptor (α/β)

			α/β	γ/δ	
Total:			95 %	5 %	
Marker:	$CD4^+$	$CD8^-$	66 %	< 1 %	
	$CD4^-$	$CD8^+$	33 %	25 %	Weak
	$CD4^-$	$CD8^-$	< 1 %	70 %	
	$CD4^+$	$CD8^+$	< 1 %	< 12 %	

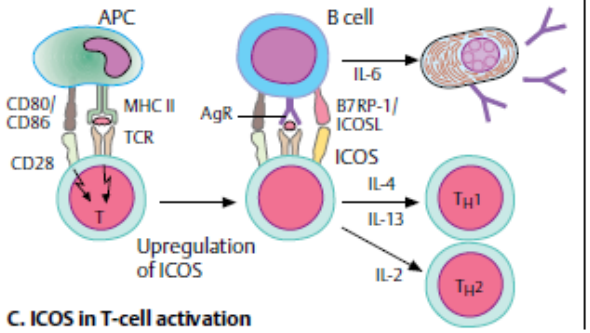
E. Distribution of α/β and γ/δ T cells



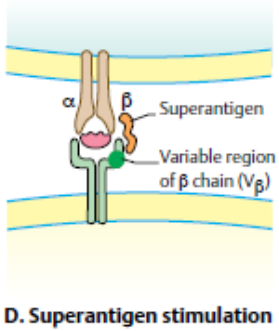
A. Molecules involved in T cell – APC interaction



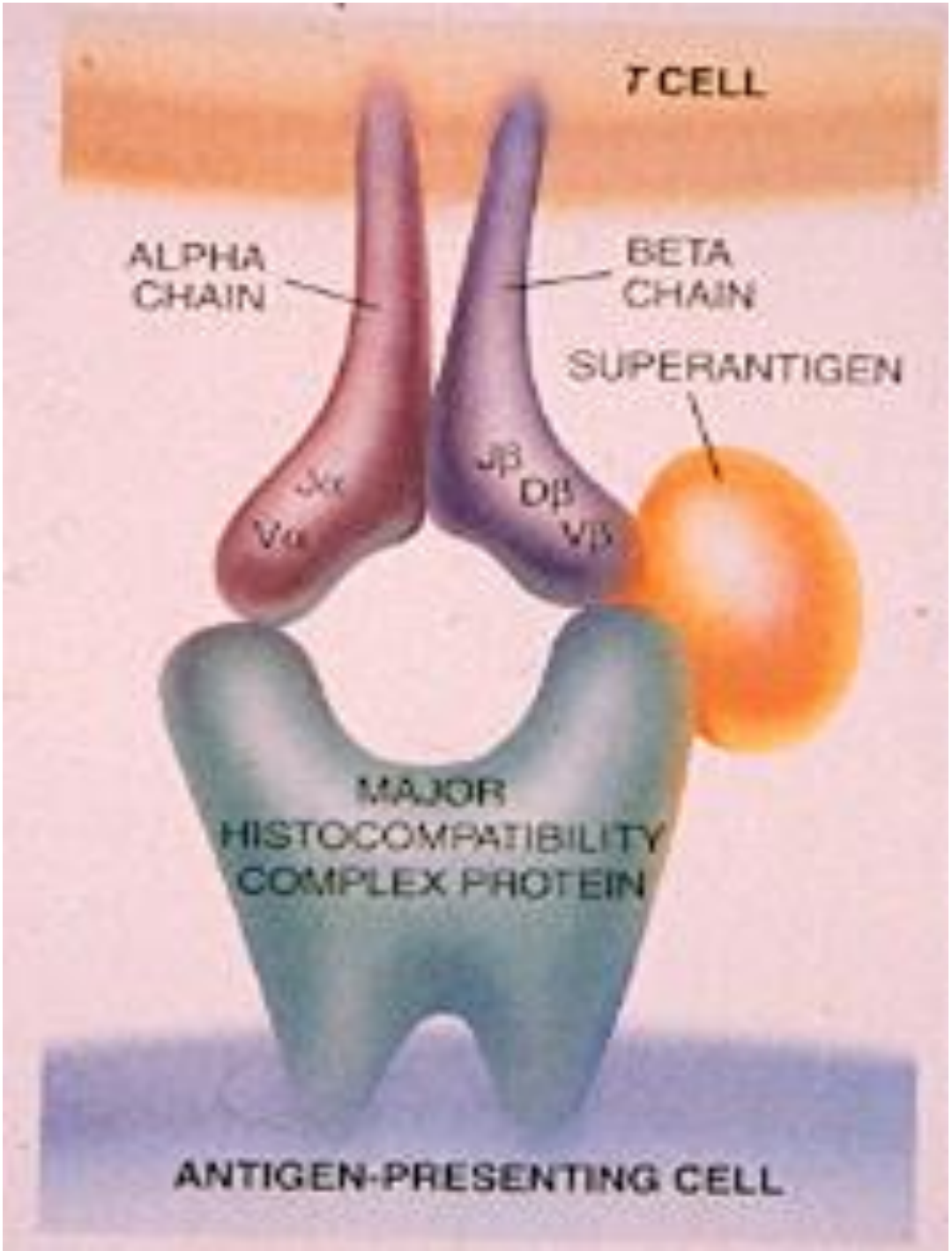
B. Several signals needed for T-cell activation



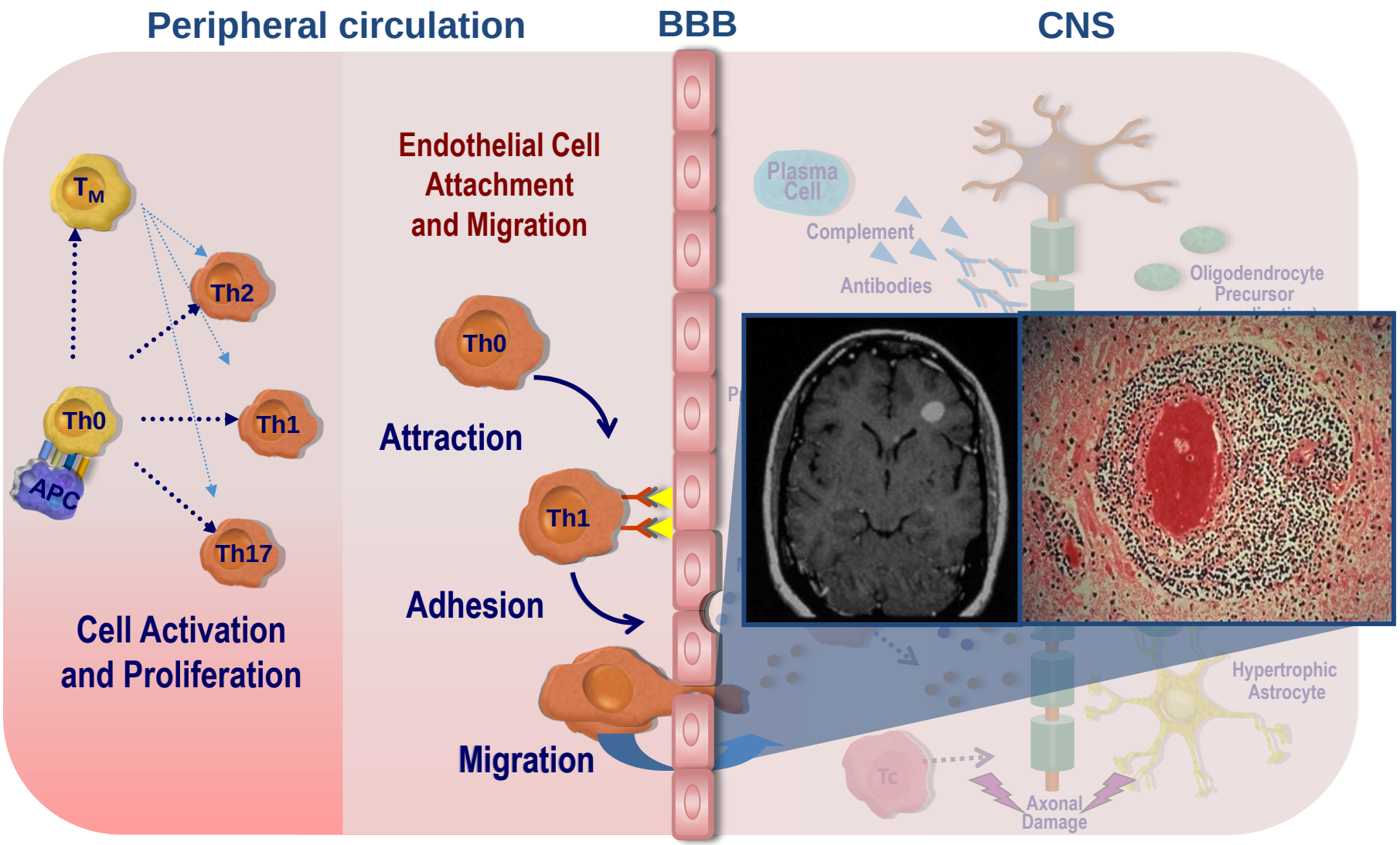
C. ICOS in T-cell activation



D. Superantigen stimulation

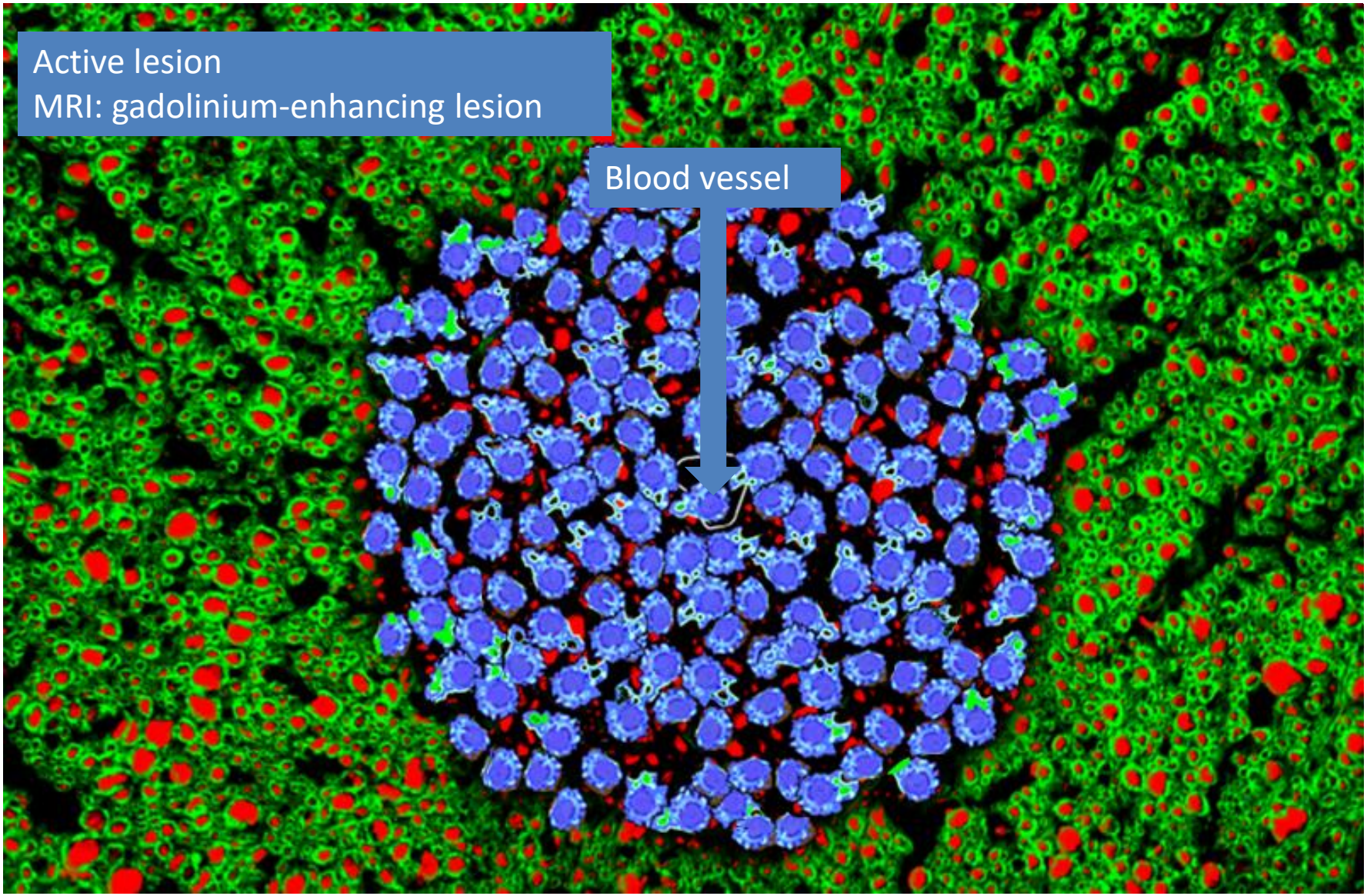

T CELL
ALPHA CHAIN
BETA CHAIN
SUPERANTIGEN
Jβ
Dβ
Vβ
MAJOR HISTOCOMPATIBILITY COMPLEX PROTEIN
ANTIGEN-PRESENTING CELL

Immune Cells Migrate into the CNS



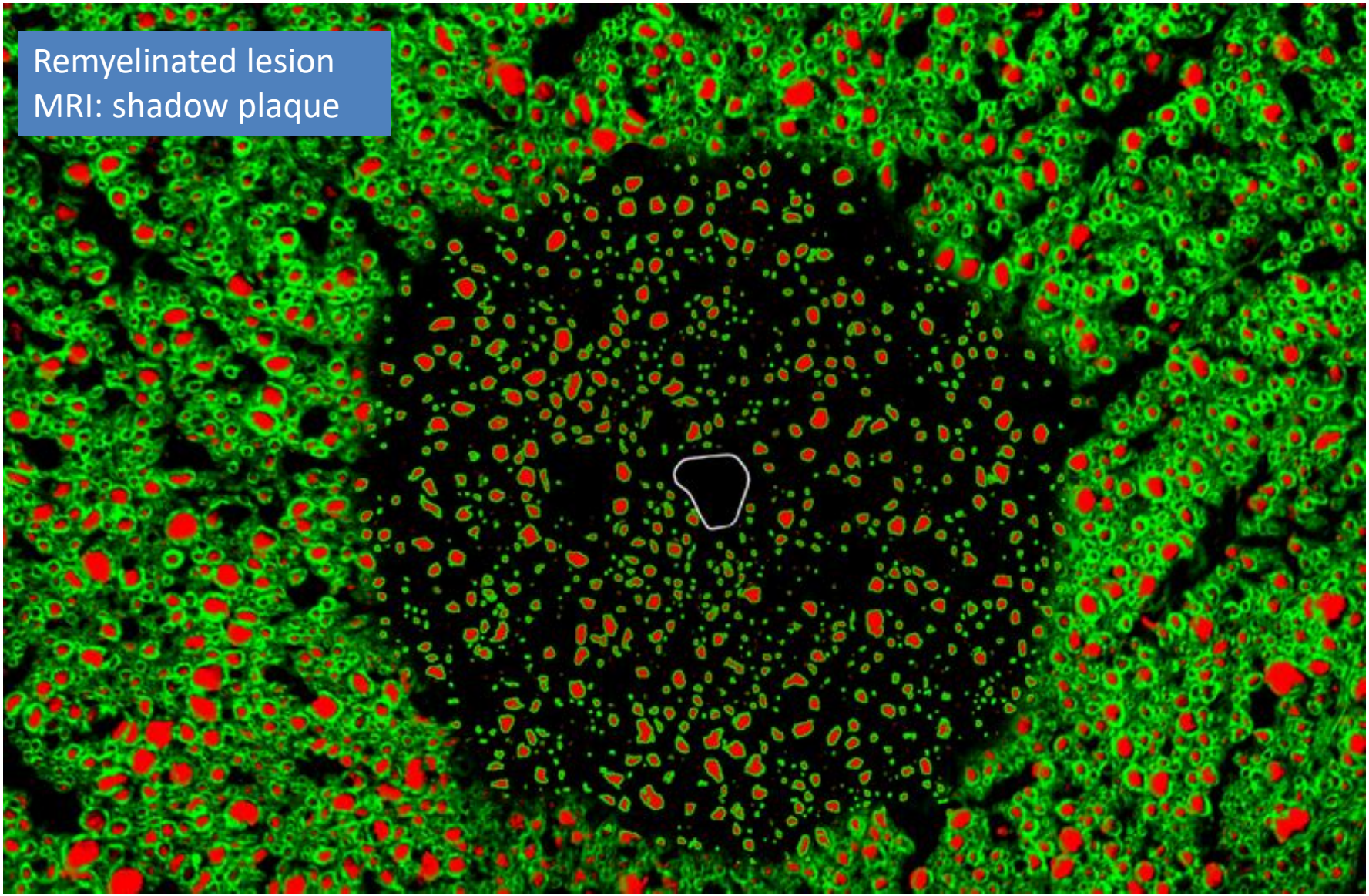
Compston A, et al, eds. *McAlpine's Multiple Sclerosis*. 4th ed. Philadelphia, PA: Churchill Livingstone, Elsevier; 2006;
Frohman EM, et al. *N Engl J Med.* 2006;354(9):942-955; Hawkins BT, Davis TP. *Pharmacol Rev*. 2005;57(2):173-185;
Lopez-Diego RS, Weiner HL. *Nat Rev Drug Discov.* 2008;7(11):909-925; Noseworthy JH, et al. *N Engl J Med*. 2000;343(13): 938-952;
Wong AD, et al. *Front Neuroeng*. 2013;6:7; Wiendl H, Kieseier BC. *Expert Opin Investig Drugs.* 2003;12(4):689-712; Yong VW. *Neurology.* 2002;59(6):802-808.

Lesion Formation: Macrophages Destroy Myelin



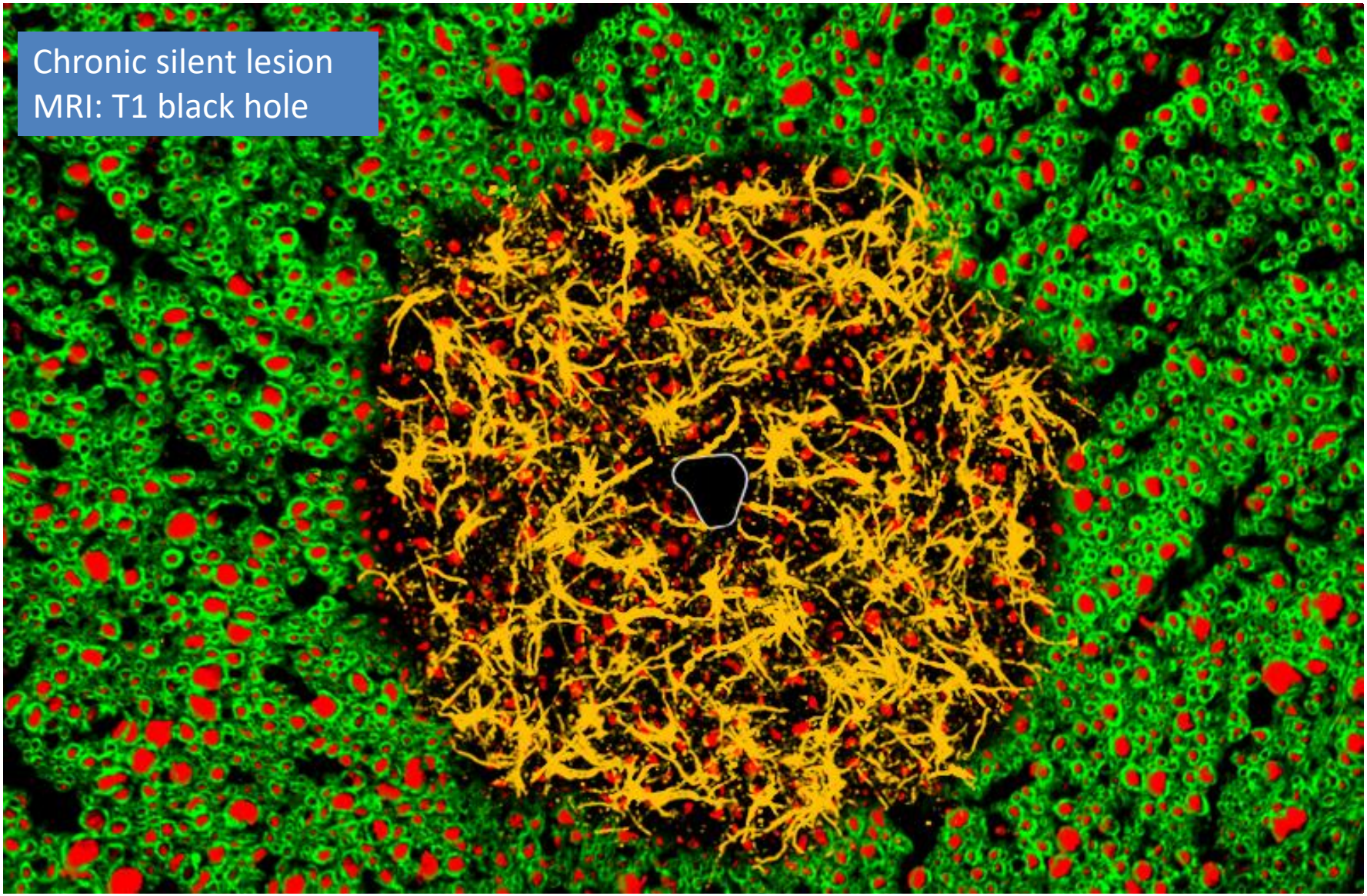
Courtesy Bruce Trapp. Frohman EM, et al. *N Engl J Med.* 2006;354(9):942-955.

Lesion Formation: Axon Damage and Remyelination



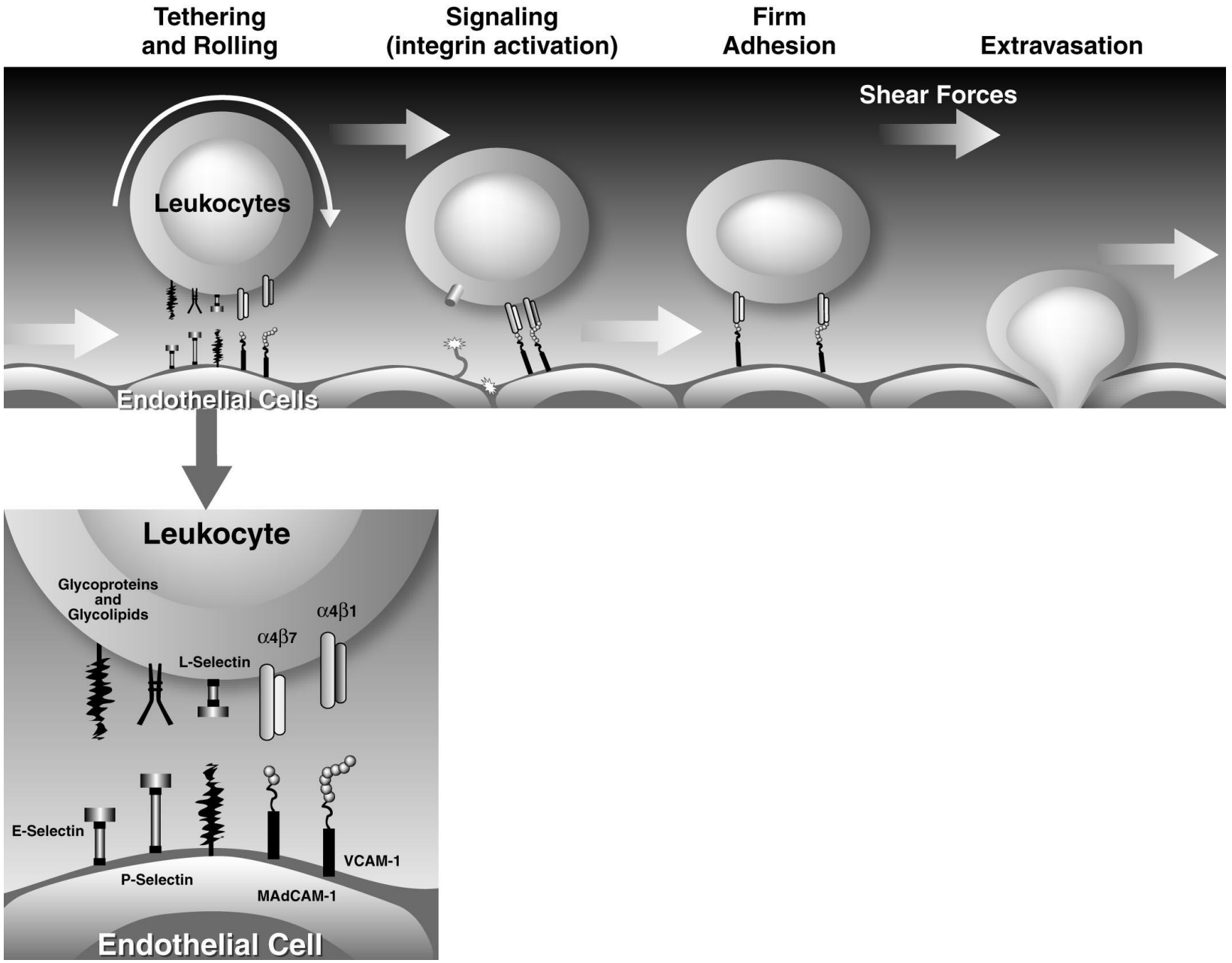
Courtesy Bruce Trapp. Frohman EM, et al. *N Engl J Med.* 2006;354(9):942-955.

Lesion Formation: Astrocytic Scar Formation



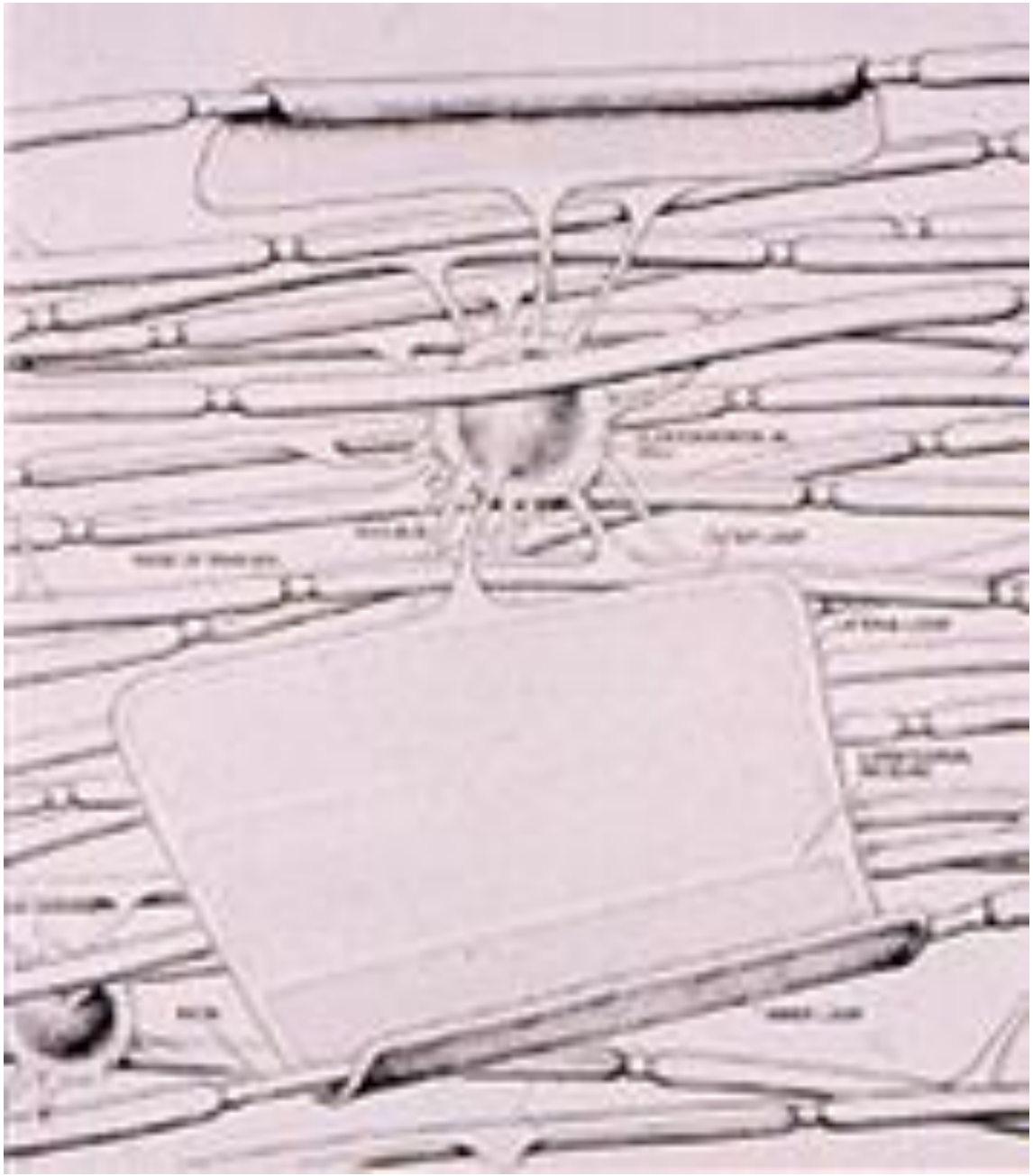
Axon Myelin Astrocyte

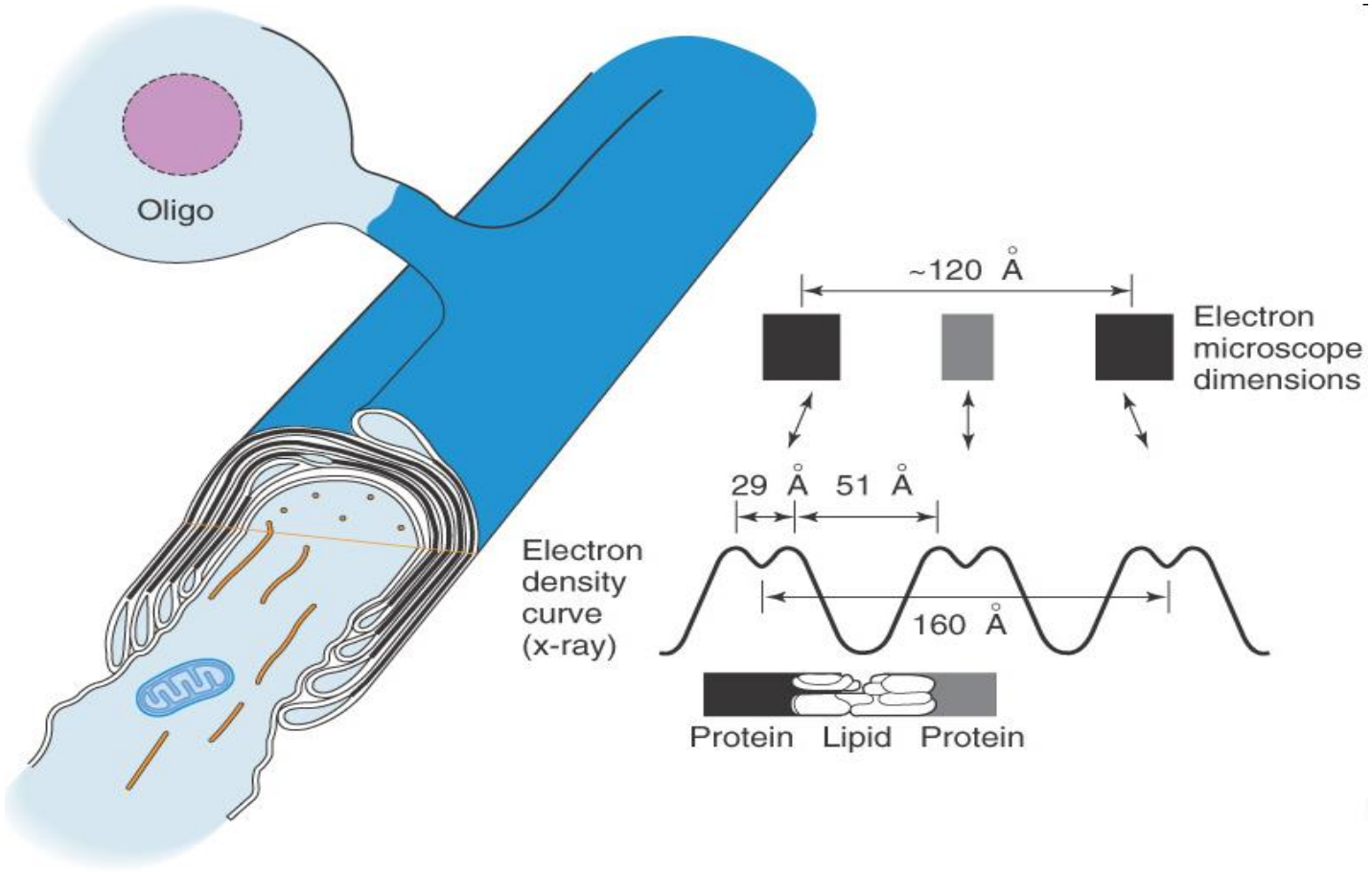
Courtesy Bruce Trapp. Frohman EM, et al. *N Engl J Med.* 2006;354(9):942-955.



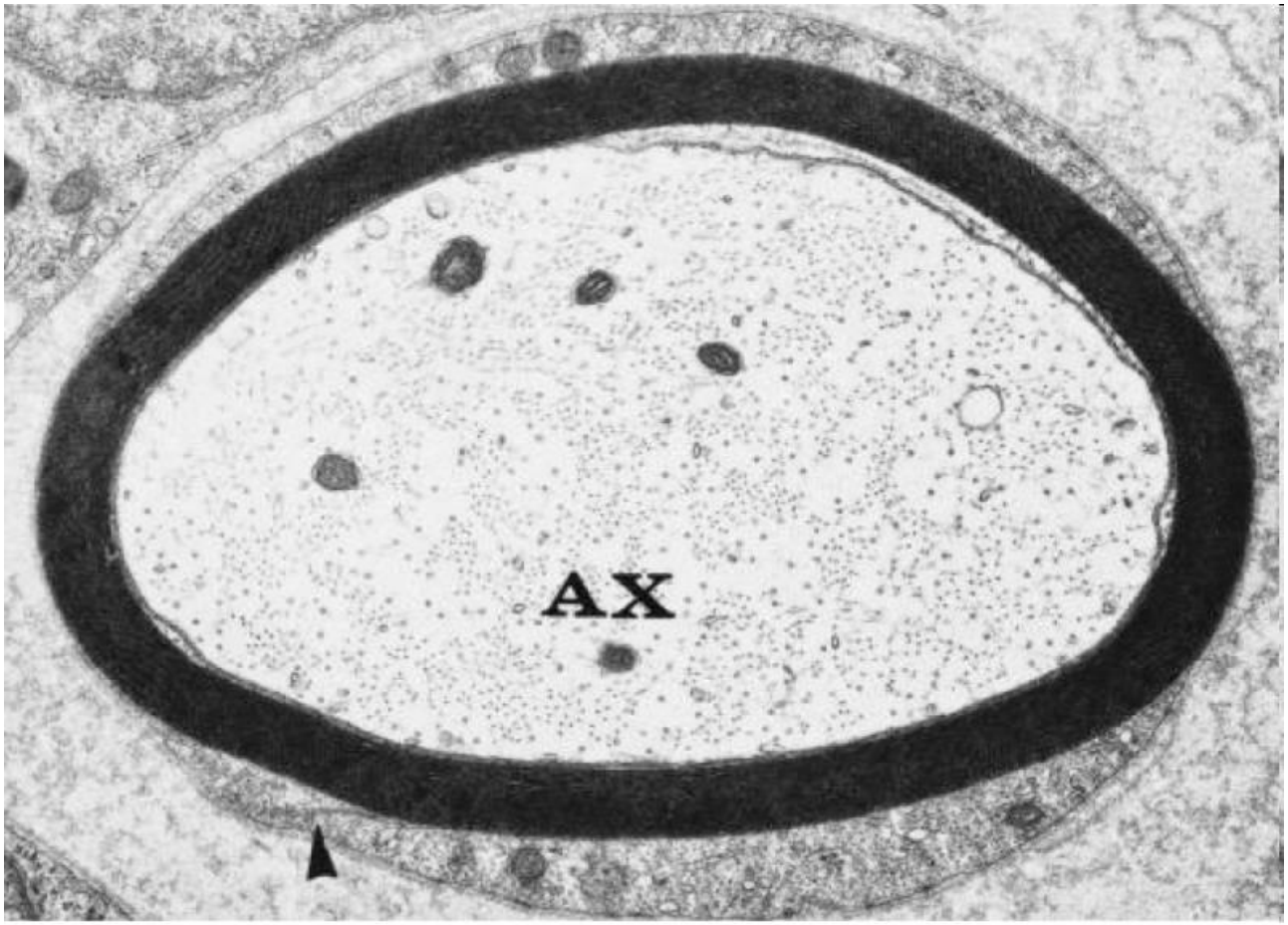
Hartung 2006

- Νοσος του Κεντρικου Νευρικου Συστηματος
- Χαρακτηριζεται από την διασπαρτη παρουσια απομυελινωτικων πλακων στηνλευκη ουσια του Εγκεφαλου και Νωτιαιου Μυελου
- Οι απομυελινωτικη πλακα είναι περιοχη της λευκης ουσιας οπου ελλειπει η μυελινη ενώ διατηρουνται οι αξονες
- Η τοπογραφικη διασπορα των πλακων καθοριξει την κλινικα συμτωματα της νοσου

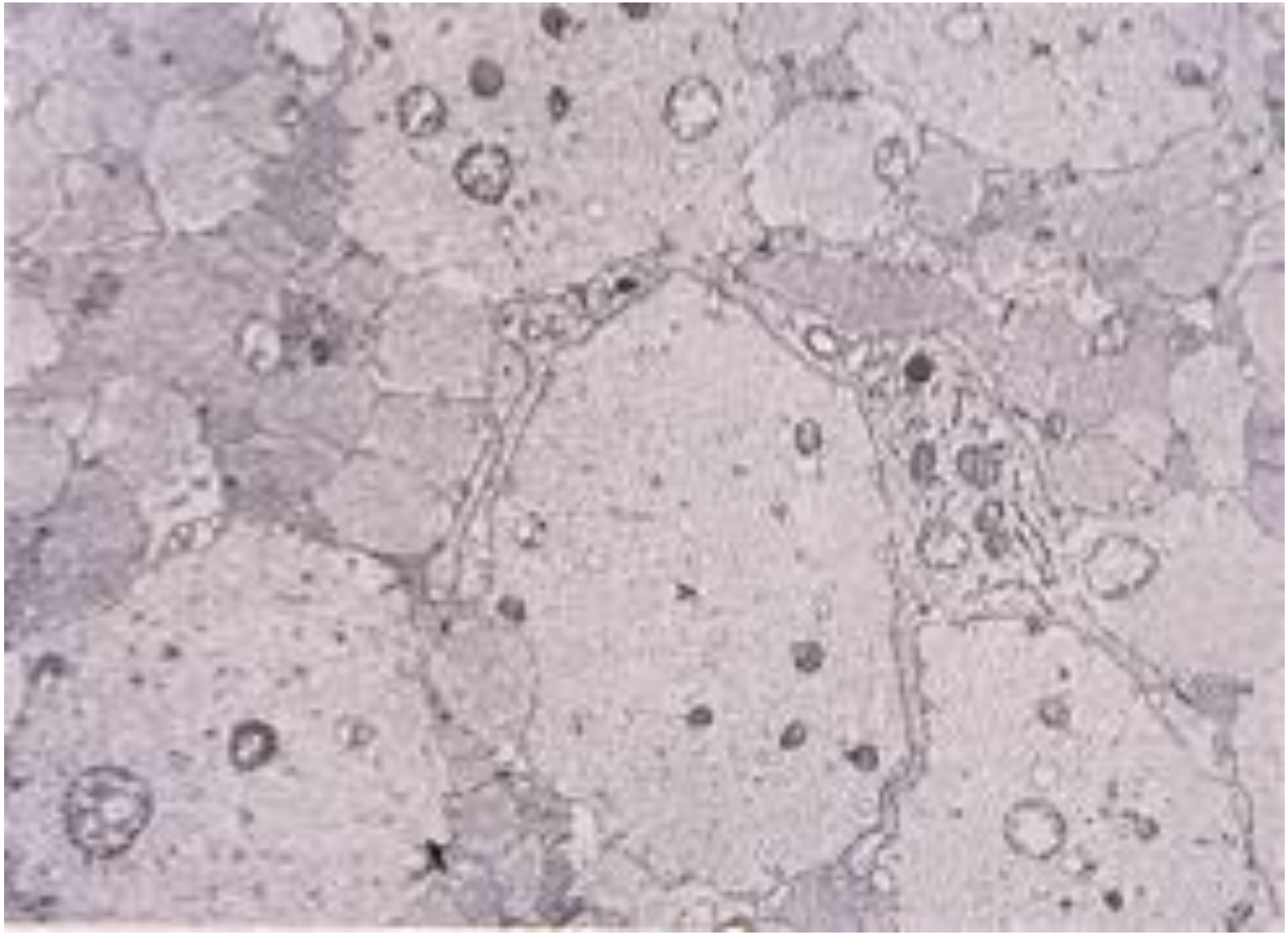




(Adapted with permission from Norton, W. T. The myelin sheath. In E. S. Goldensohn and S. H. Appel (eds), *Scientific Approaches to Clinical Neurology.* Philadelphia: Lea & Febiger, 1977, pp. 259–298.)

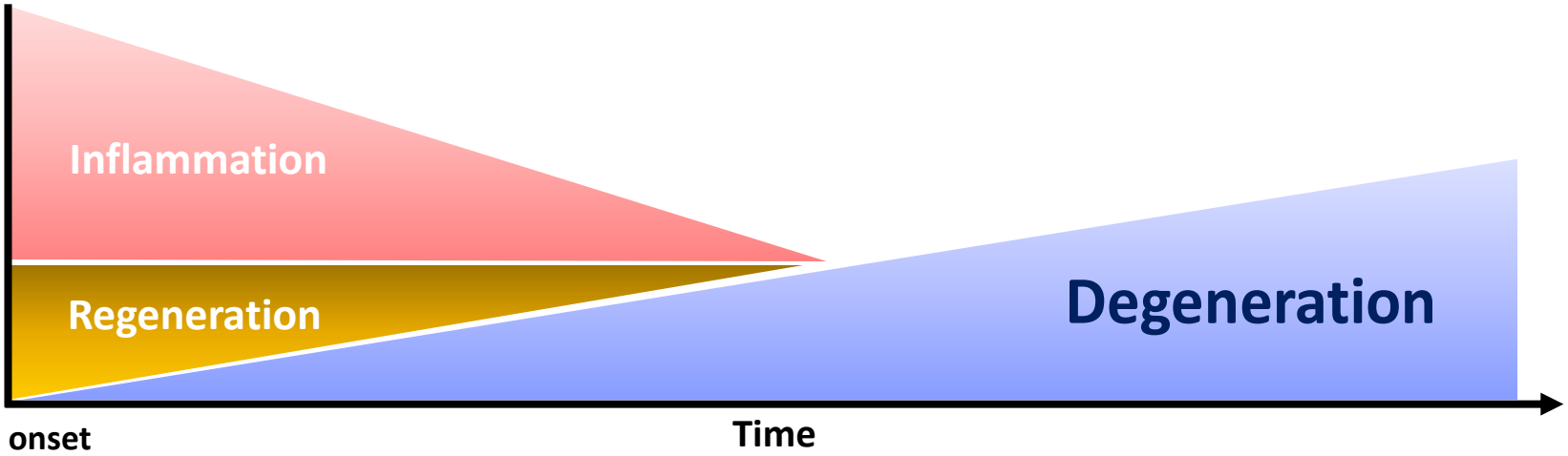


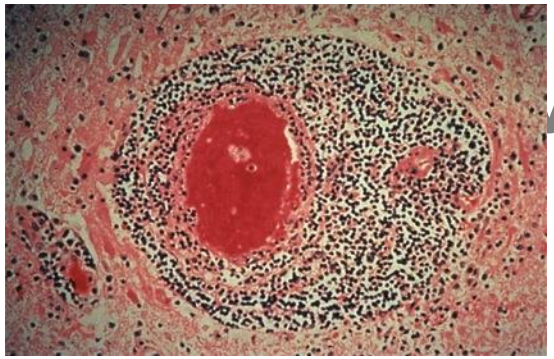
(Courtesy of Dr Cedric Raine.)



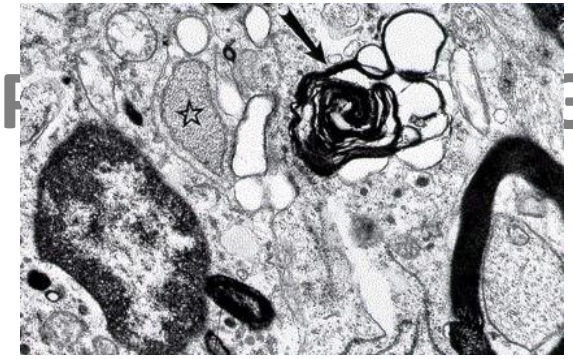
Χρονια απομυελινωτικη πλακα

Inflammatory processes occurring <u>early</u> in MS lead to demyelination and axonal loss

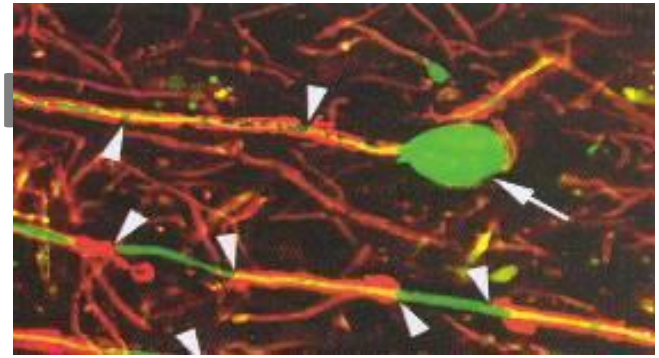




Inflammation



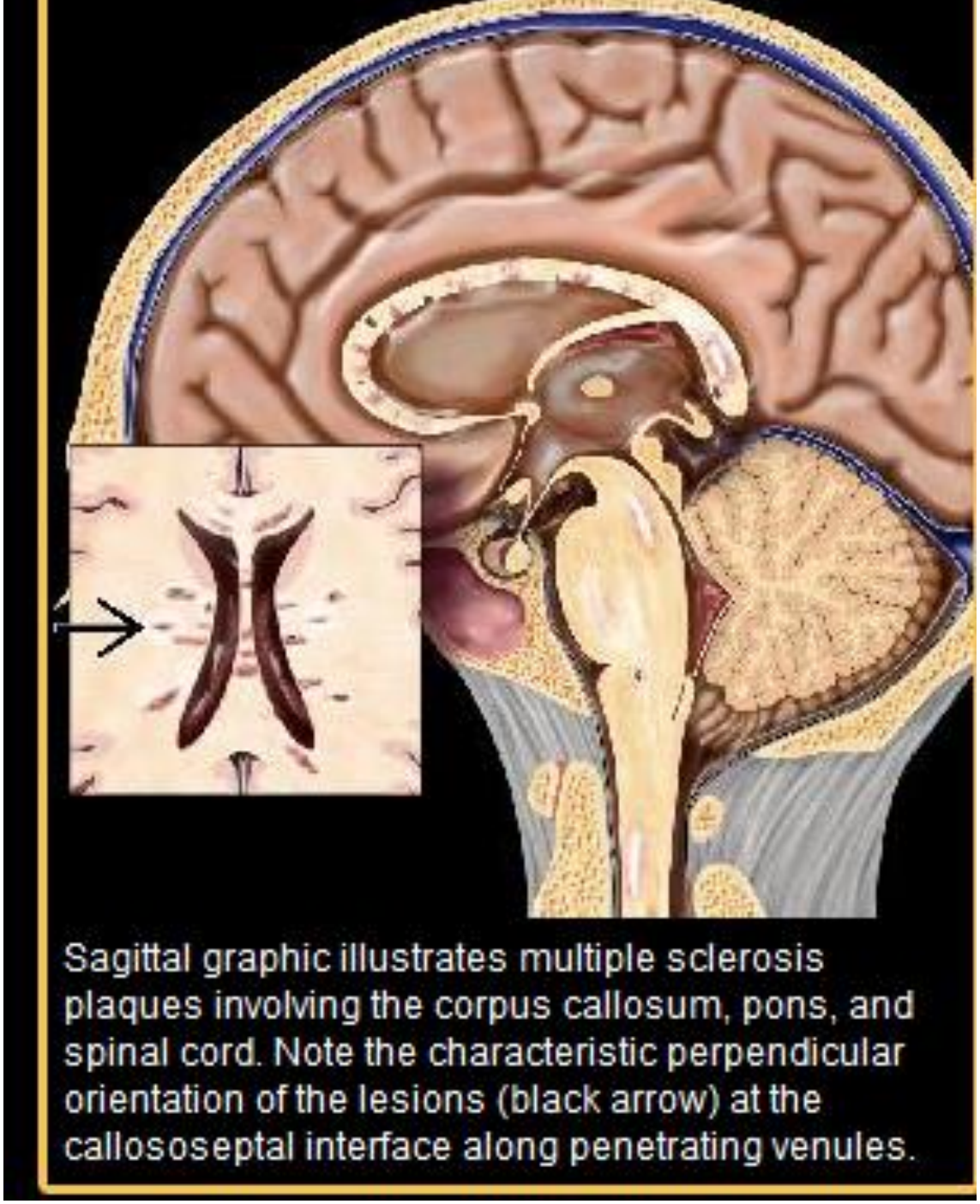
Demyelination



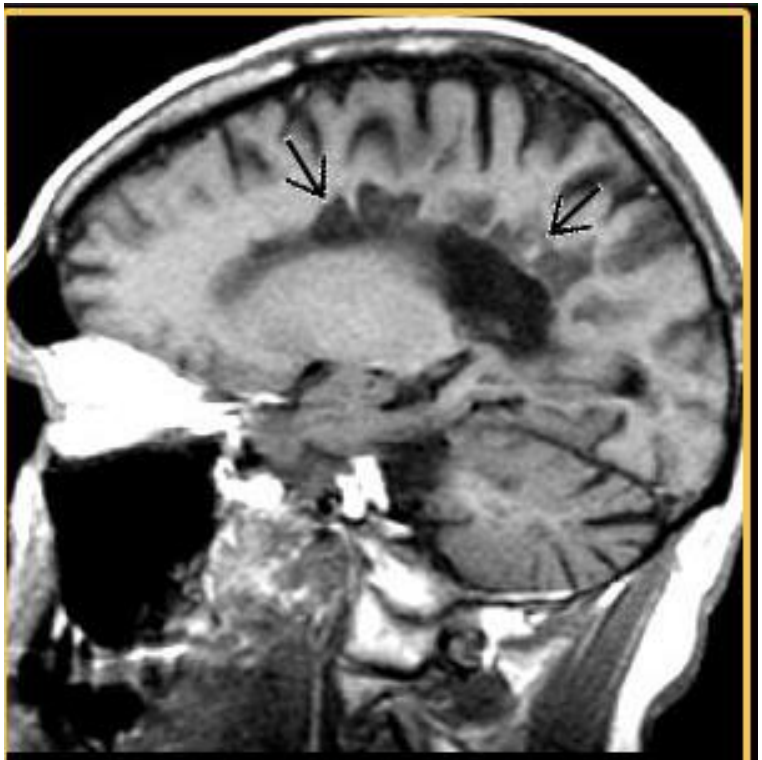
Axonal loss

Aminoff MJ, et al, eds. *Handbook of Clinical Neurology*. Amsterdam, The Netherlands: Elsevier BV; 2013. Barnes MP, Good CD, eds. *Neurological Rehabilitation*; vol 10 (3rd series); Cifelli A, et al. *Ann Neurol.* 2002;52(5):650-653; Compston A, Coles A. *Lancet.* 2008;372(9648):1502-1517; National MS Society. Exacerbations. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/exacerbations/index.aspx Accessed January 23, 2014; National MS Society. How RRMS differs from progressive courses of MS. http://www.nationalmssociety.org/about-multiple-sclerosis/relapsing-ms/relapsing-remitting-ms-rrms/how-rrms-differs-from-progressive-courses-of-ms/index.aspx Accessed January 23, 2014; Trapp BD, et al. *Neuroscientist.* 1999;5(1):48-57.

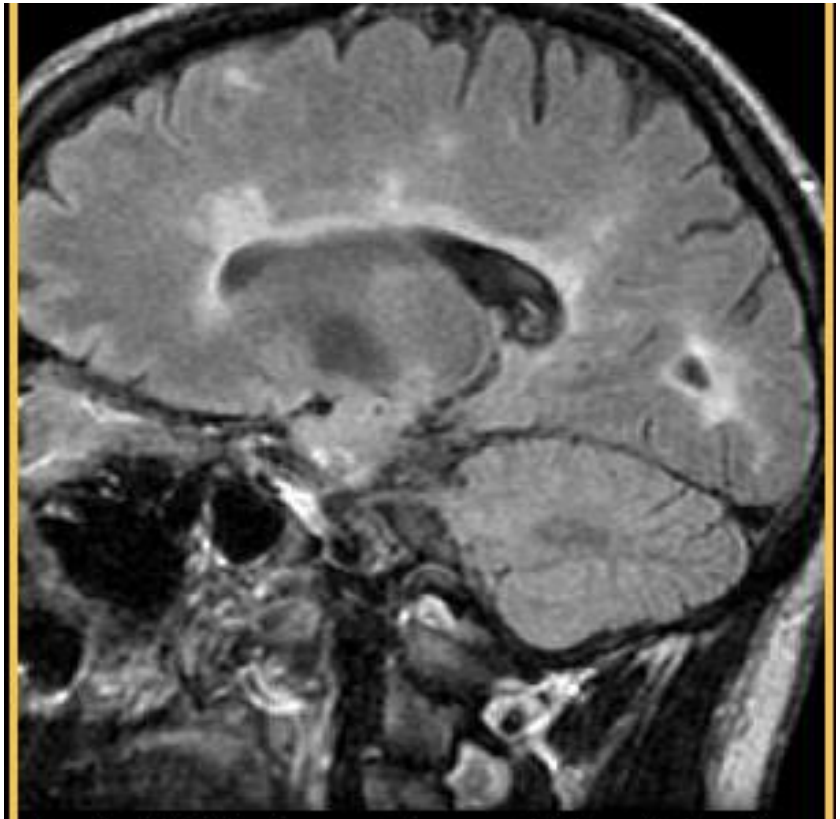
MS,TOPOGRAPHY



Sagittal graphic illustrates multiple sclerosis plaques involving the corpus callosum, pons, and spinal cord. Note the characteristic perpendicular orientation of the lesions (black arrow) at the callososeptal interface along penetrating venules.



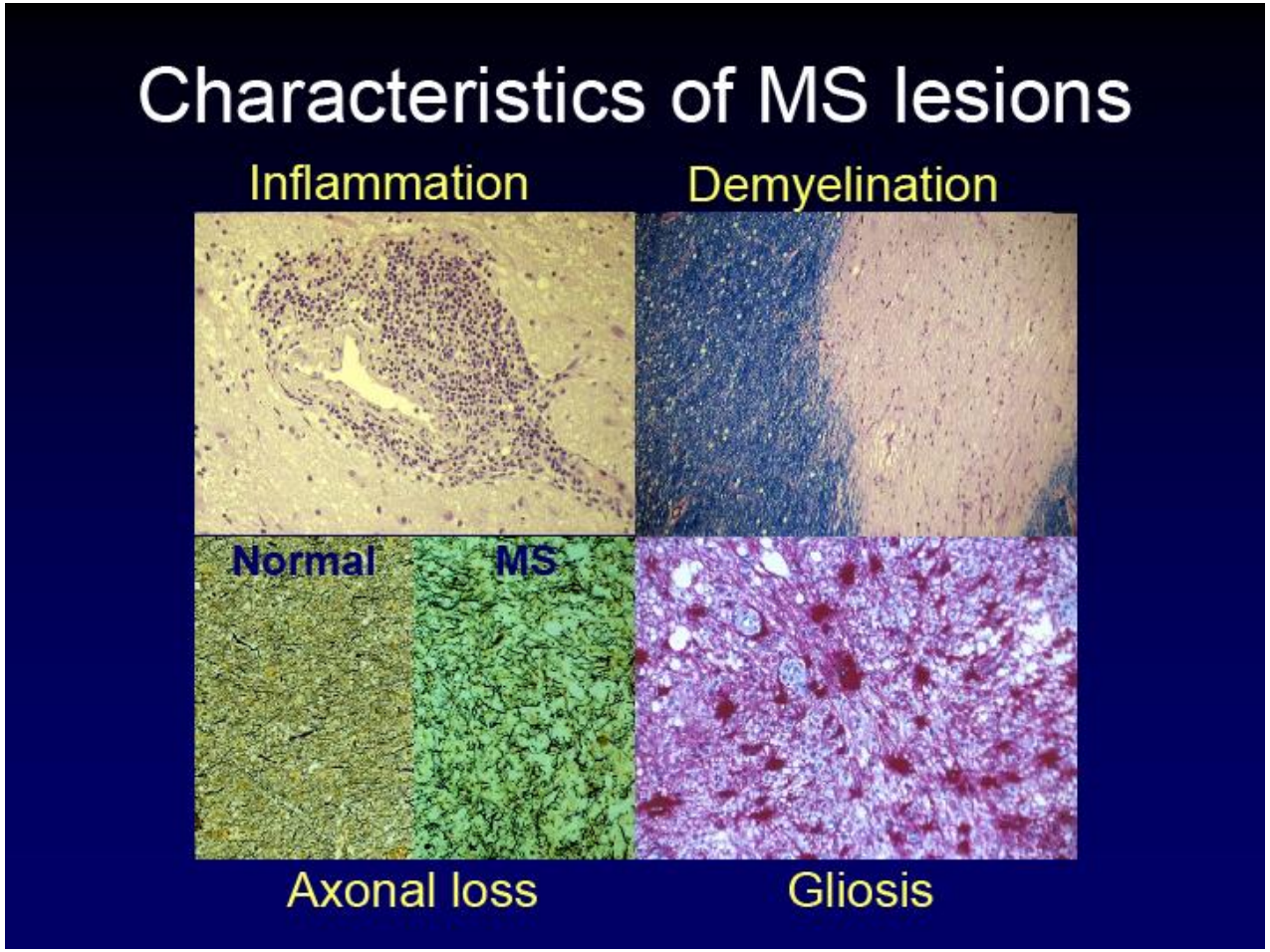
Sagittal T1WI MR shows multiple hypointense lesions ("black holes") in the deep white matter (black arrow) related to axonal destruction. Note the associated moderate ventricular and sulcal enlargement.



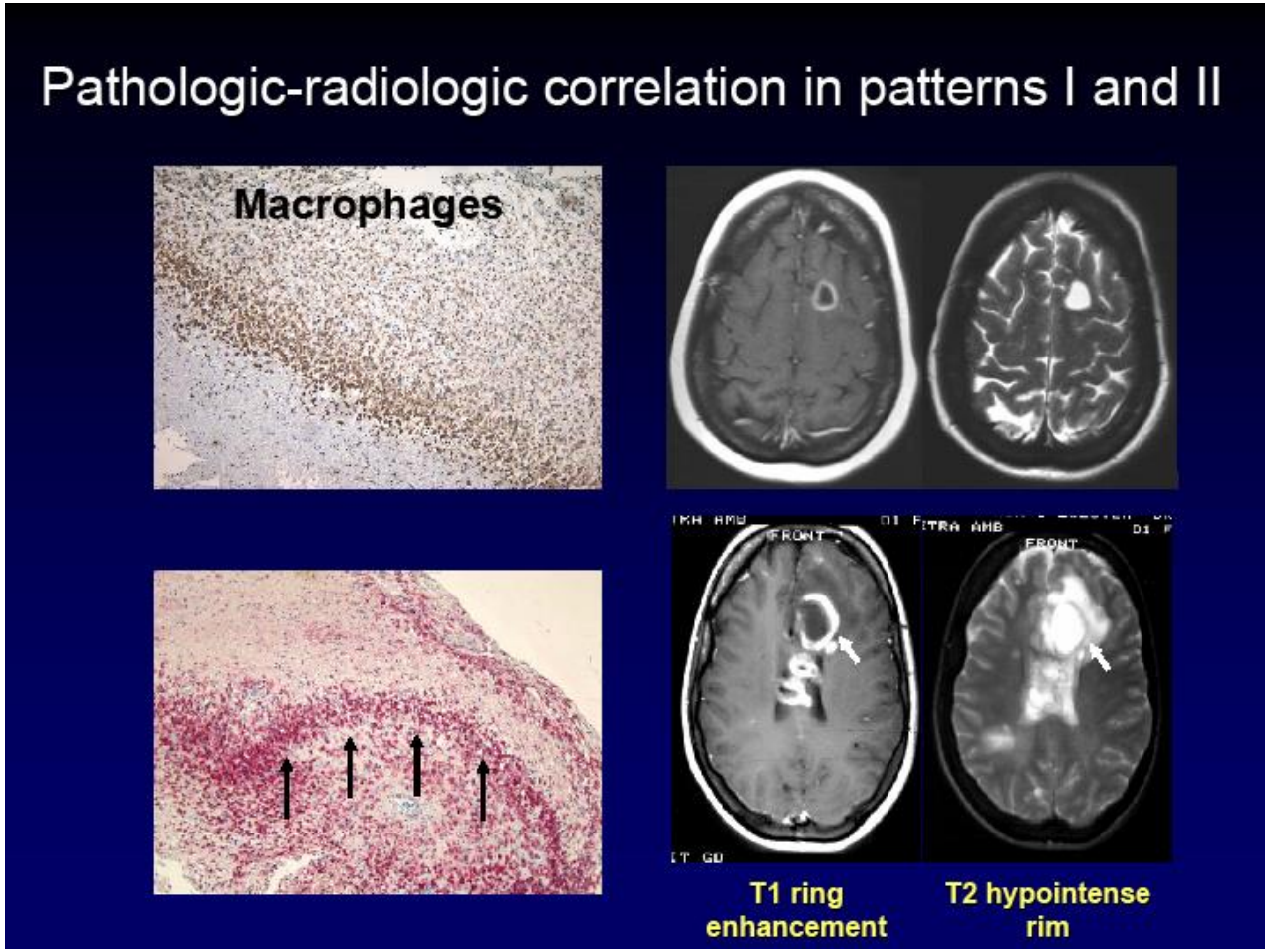
Sagittal FLAIR shows callososeptal hyperintensities radiating from the lateral ventricles with a typical perpendicular orientation, characteristic of multiple sclerosis.

MS ,HISTOPATHOLOGY

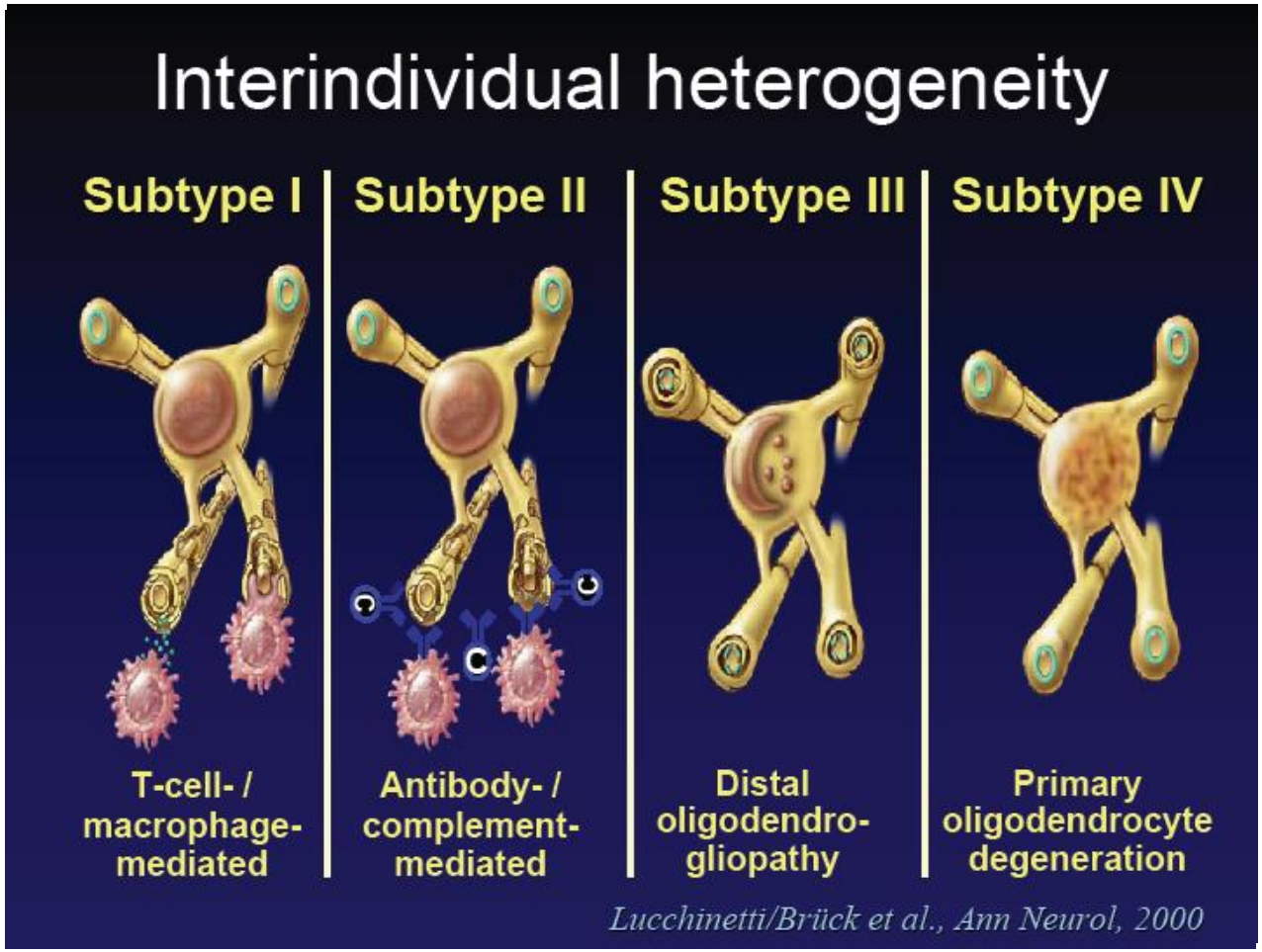
MS -Neuropathology



MRI Neuropathological corelations

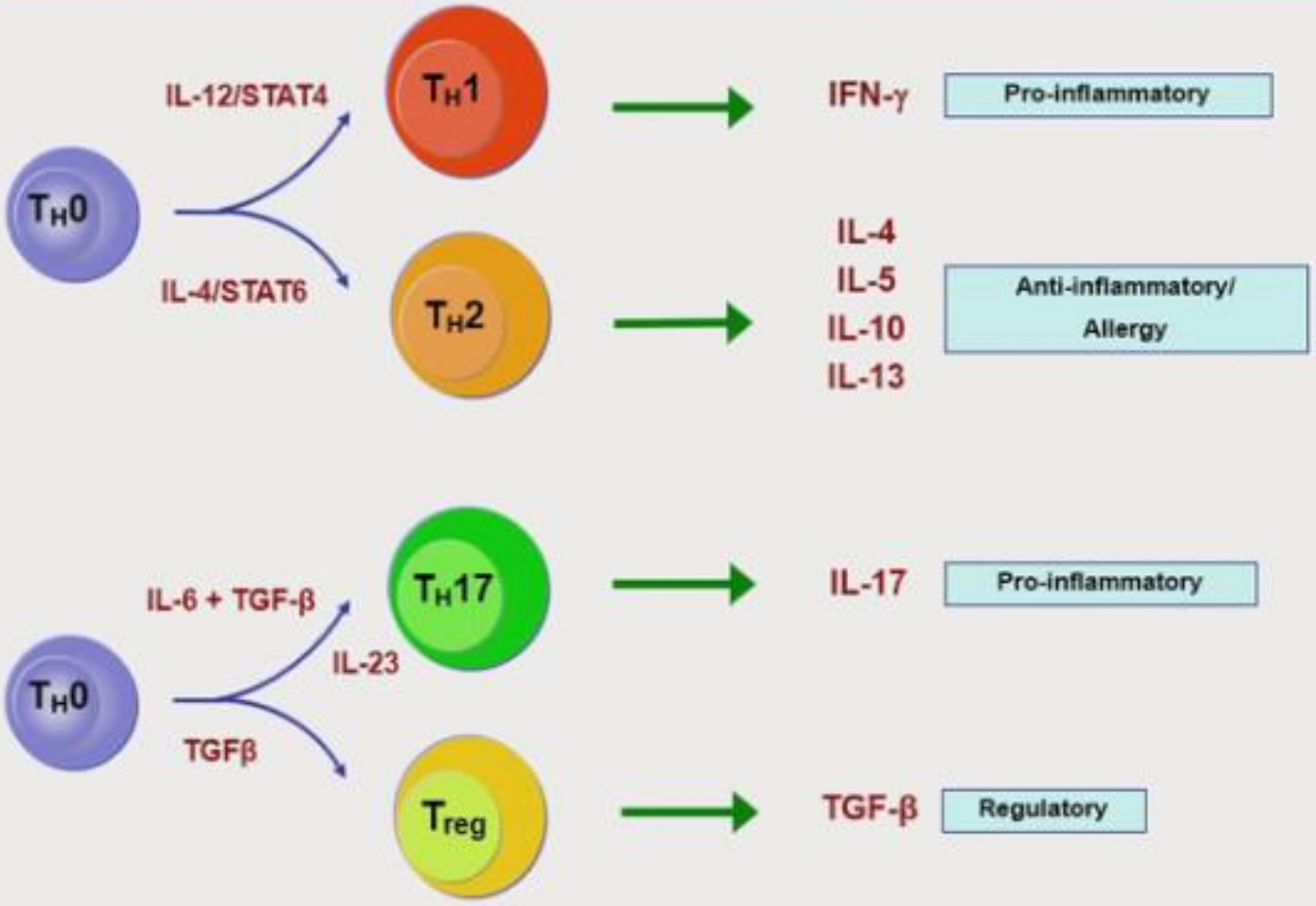


Interindividual heterogeneity



Lucchinetti/Brück et al., Ann Neurol, 2000

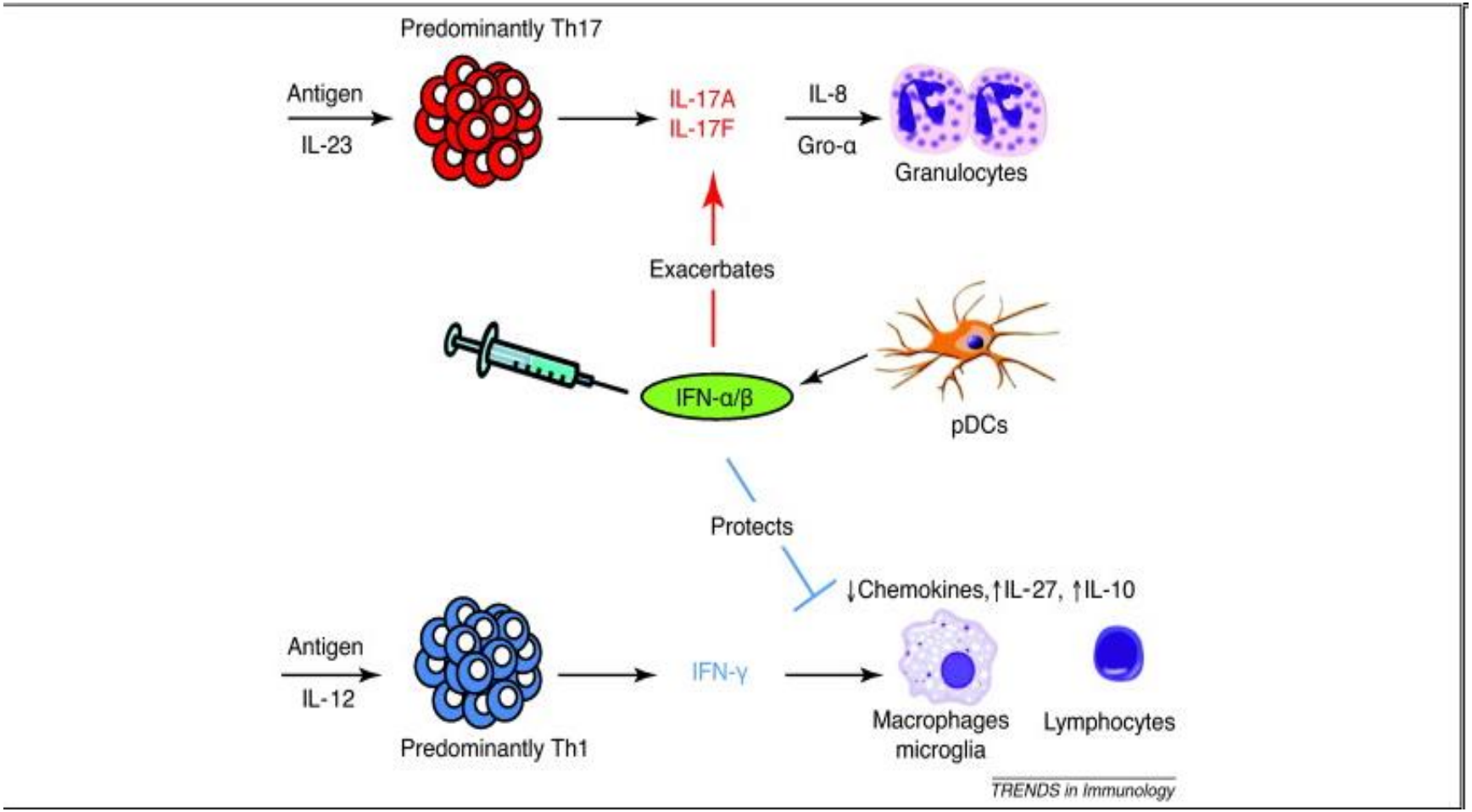
Helper T cell differentiation



IL-17 cytokine

- CD4+,CD8+,CD3+,express IL-17 In active MS lessions but not in inactive lessions .[Tzartos JS etal 2007]

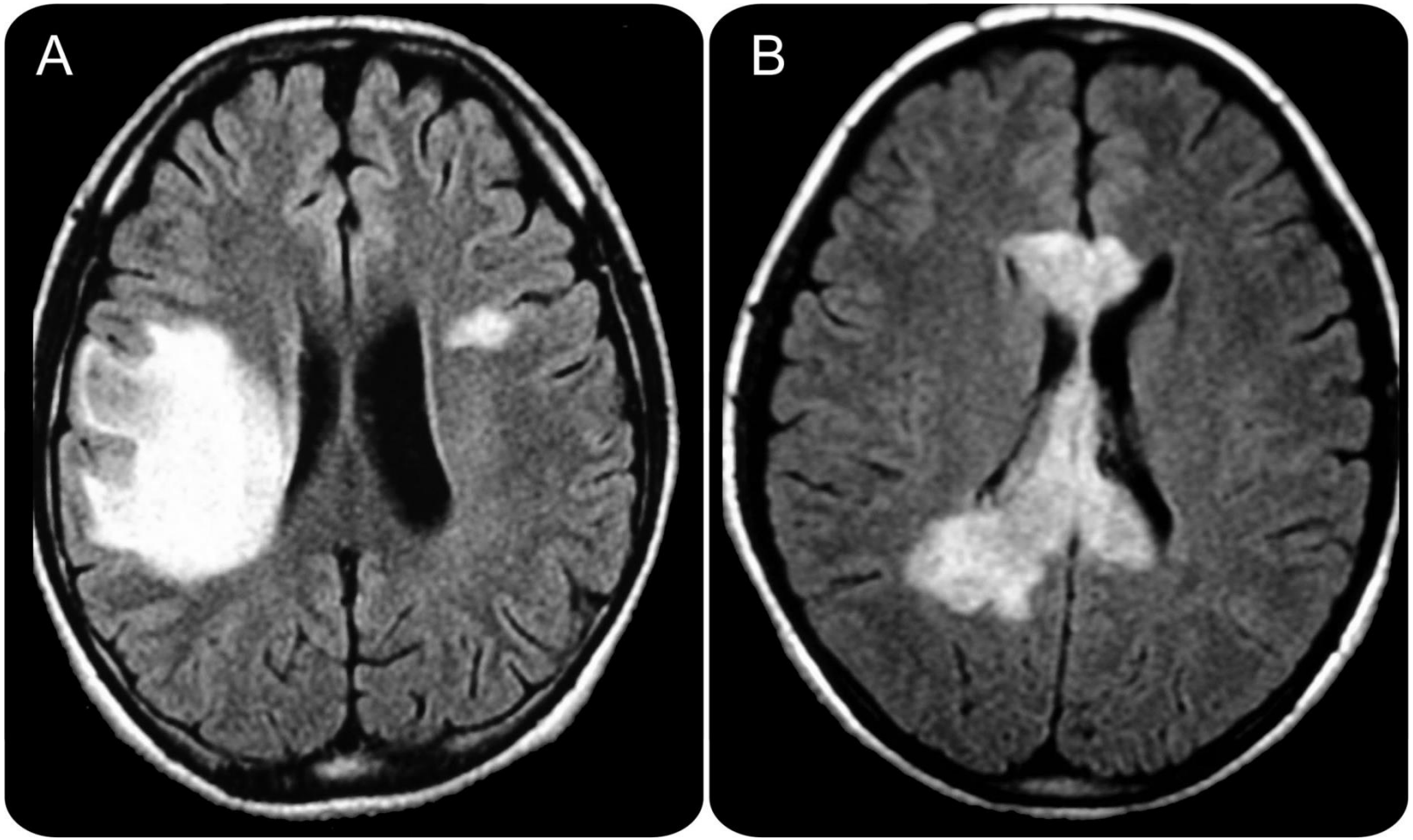
- IL-17 expressed in NAWM
- IL-17 in MS-CSF



Axtel etal 2010

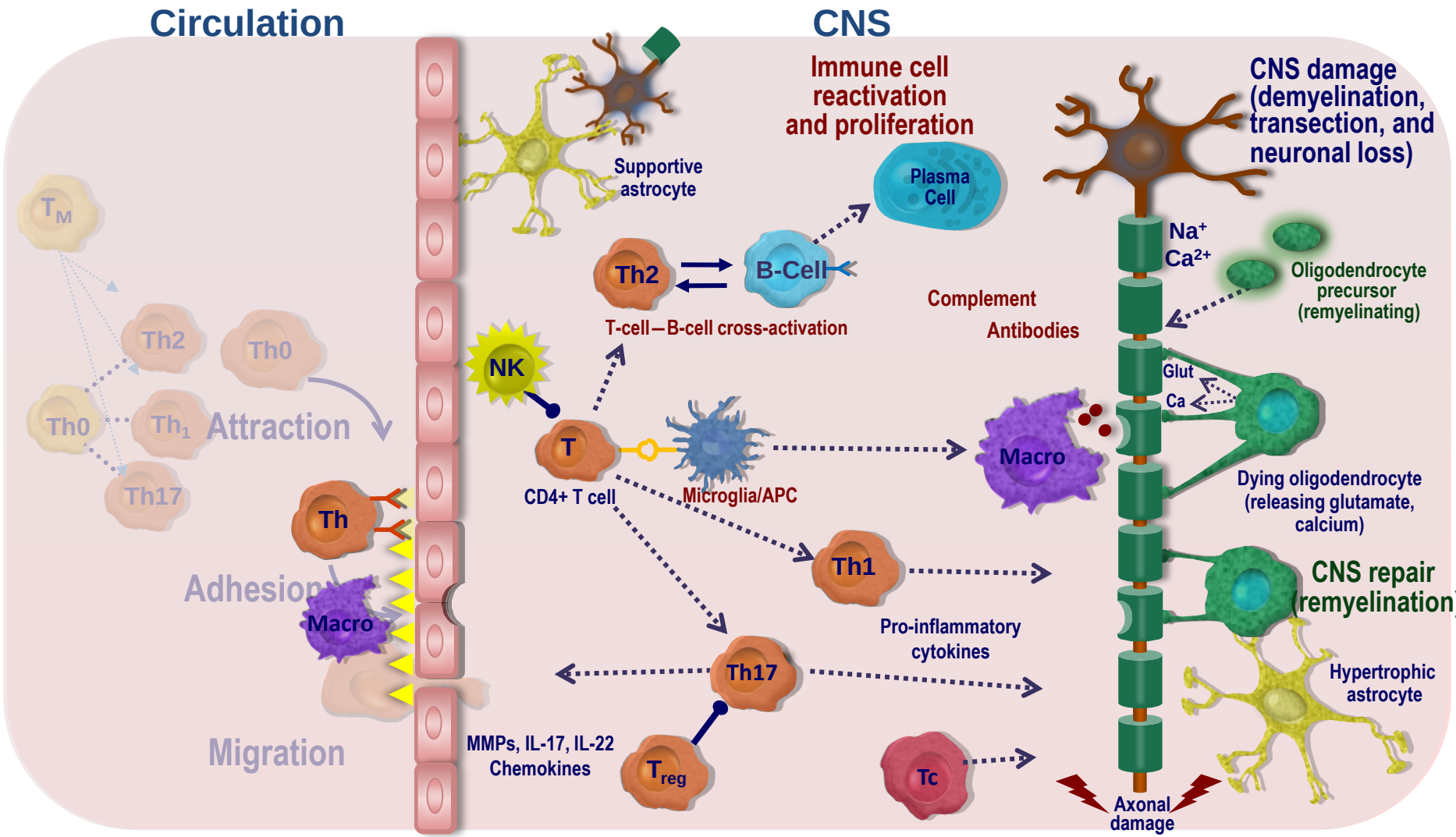
- Further information derives from NMO where the high levels of IL-17 promote local expression IL-8,G-CSF, and macrophage activation.IFN-b may cause severe excacerbation

IFN-b exacerbates Japanese OPSMS within the spectrum of Neuromyelitis optica



Shimizu et al 2010

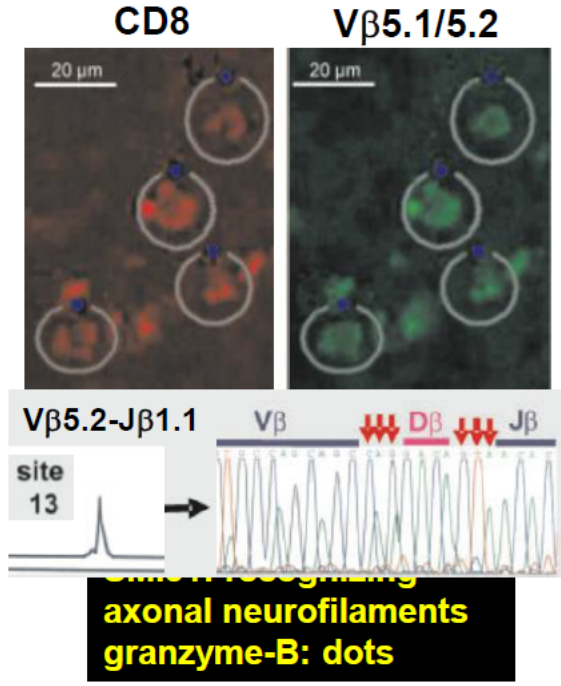
Inflammation Leads to Demyelination and Axonal Loss



Alvarez J, et al. *Biochem Biophys Acta.* 2011;1812(2):252–264; Aminoff MJ, et al, eds. *Handbook of Clinical Neurology*. Amsterdam, The Netherlands: Elsevier BV; 2013. Barnes MP, Good CD, eds. *Neurological Rehabilitation*; vol 10 (3rd series); Frohman EM, et al. *N Engl J Med.* 2006;354(9):942-955; Frohman TC, et al, Eds. *Multiple Sclerosis for the Physician Assistant : a Practical Primer*. http://www.nationalmssociety.org Published 2011. Accessed January 23, 2014; Lopez-Diego RS, Weiner HL. *Nat Rev Drug Discov.* 2008;7(11):909-925; Murphy K, et al, eds. *Janeway's Immunobiology*. 8th ed. New York, NY: Garland Science; 2012; Wiendl H, Kieseier BC. *Expert Opin Investig Drugs*. 2003;12(4):689-712; Yong VW. *Neurology.* 2002;59(6):802-808;

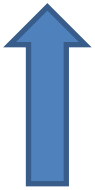
A pathogenic role for CD8 T cells in MS ?

- In mice, myelin-specific CD8 T cells **transfer EAE**.
- **CD8⁺ T cells dominate** in MS lesions.
- **Oligoclonal expansion** of CD8⁺ T cells in the CSF & lesions of MS patients.
- Contact between **granzyme+ T cell** and demyelinated **axons**.



Liblau *et al.* Immunity 2002, 17: 1
Neumann *et al.* Trends Neurosci 2002, 25: 313
Junker *et al.* Brain 2007, 130: 2798.

Multiple sclerosis (MS) is an inflammatory demyelinating disease where T cells attack the brain and the spinal cord. It is known that often particular T-cell clones are expanded in the target tissue, but it is still unknown, whether identical T-cell clones are present at distinct anatomical sites, or whether the T-cell spectrum is locally diverse. Therefore we compared the T-cell receptor (TCR) repertoire in distinct lesions and normal-appearing white matter (NAWM) from post-mortem brains of four MS patients. We analysed 19 lesions (inactive demyelinated, 15; slowly expanding chronic, 3; active lesions, 1) and 5 NAWM regions. The TCR β-chain repertoire was investigated by CDR3 spectratyping. For each anatomical site 325 semi-nested PCR reactions were performed. About 800 Vβ-NDN-Jβ combinations were sequenced. Each of the four patients had distinct T-cell clones that were present in more than two anatomically distinct regions. These clones were not restricted to lesions, but were also present in NAWM. Some clones were present in all investigated lesions, and additionally, in NAWM sites. A single T-cell clone was detected in nine different sites in one patient. None of the clones was shared among different patients. Thus, pervasive T-cell clones exist in distinct regions of MS brain, and these clones are 'private' (unique) to individual patients. Analysis of the hypervariable NDN region revealed 'silent' nucleotide exchanges, i.e. nucleotide exchanges that code for identical amino acids. Such silent nucleotide exchanges suggest that the corresponding T-cell clones were recruited and stimulated by particular antigens. To attribute some of the pervasive clones to particular T-cell subsets, we isolated individual CD8+ T cells from cryosections by laser microdissection and characterized their TCR by single-cell PCR. These experiments revealed that at least some of the pervasive T-cell clones belonged to the CD8+ compartment, supporting the pathogenic relevance of this T-cell subset.

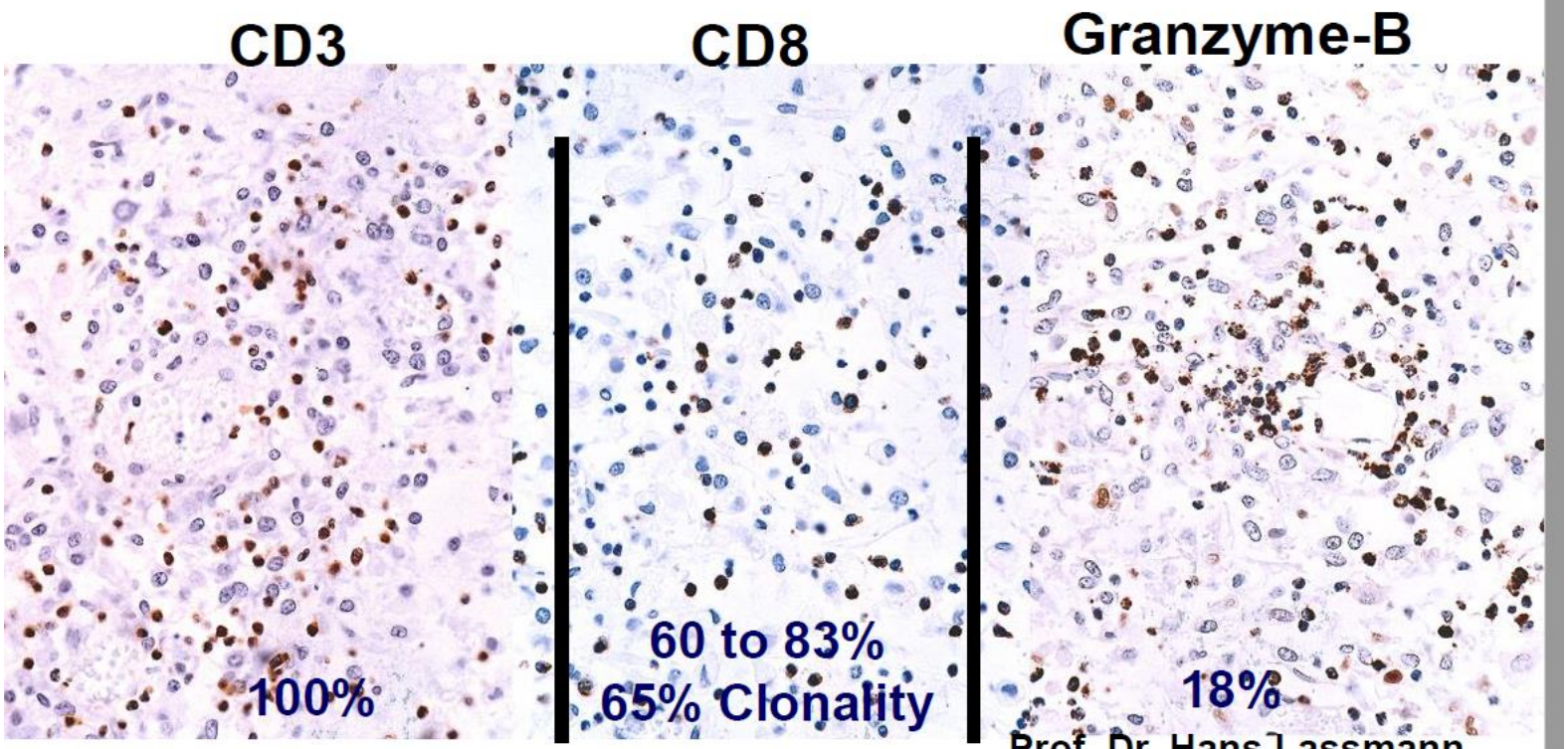


A Junker 2007

Discussion

The main findings of our comprehensive survey of the TCR β-chain repertoire in four MS whole brain specimens are as follows: (a) identical T-cell clones were detected in separate brain regions, including NAWM, although the TCR repertoire in each brain was oligoclonally diverse; (b) some spectratyping-defined TCR sequences identified in individual tissue-infiltrating T cells were CD8+ by immunohistochemical staining; (c) several TCR sequences contained silent mutations in the CDR3 region, suggesting antigen-driven recruitment and (d) the TCR repertoire was strictly private to each patient, although some frequently occurring HLA class I and class II alleles were shared among patients.

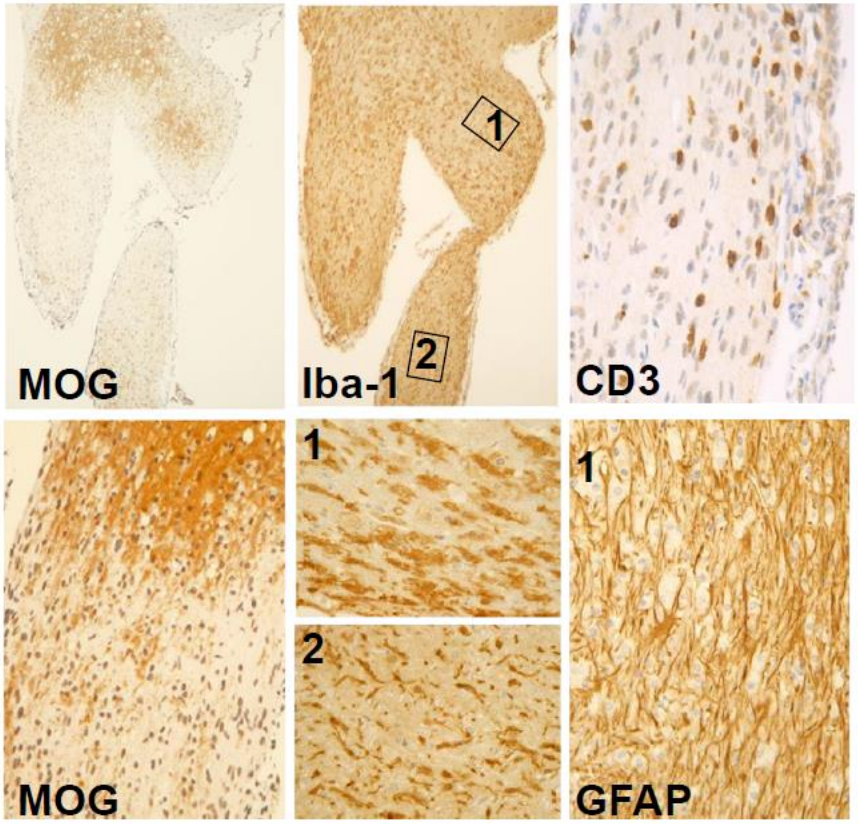
Pathogenic role for CD8 T cells in multiple sclerosis ?



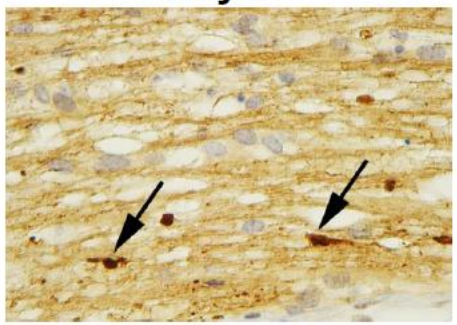
Prof. Dr. Hans Lassmann

→ Acute MS-perivascular and parenchymal inflammation dominated by $CD8^+$ T cells

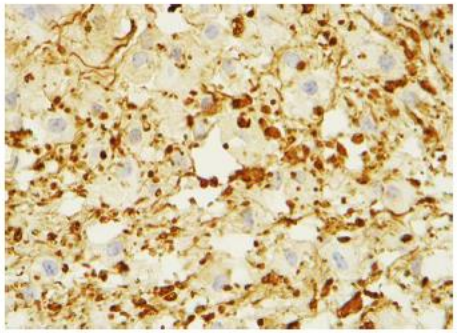
CNS damage by transfer of ‘autoreactive’ CD8 T cells targeting oligodendrocytes



Day 9



Day 18

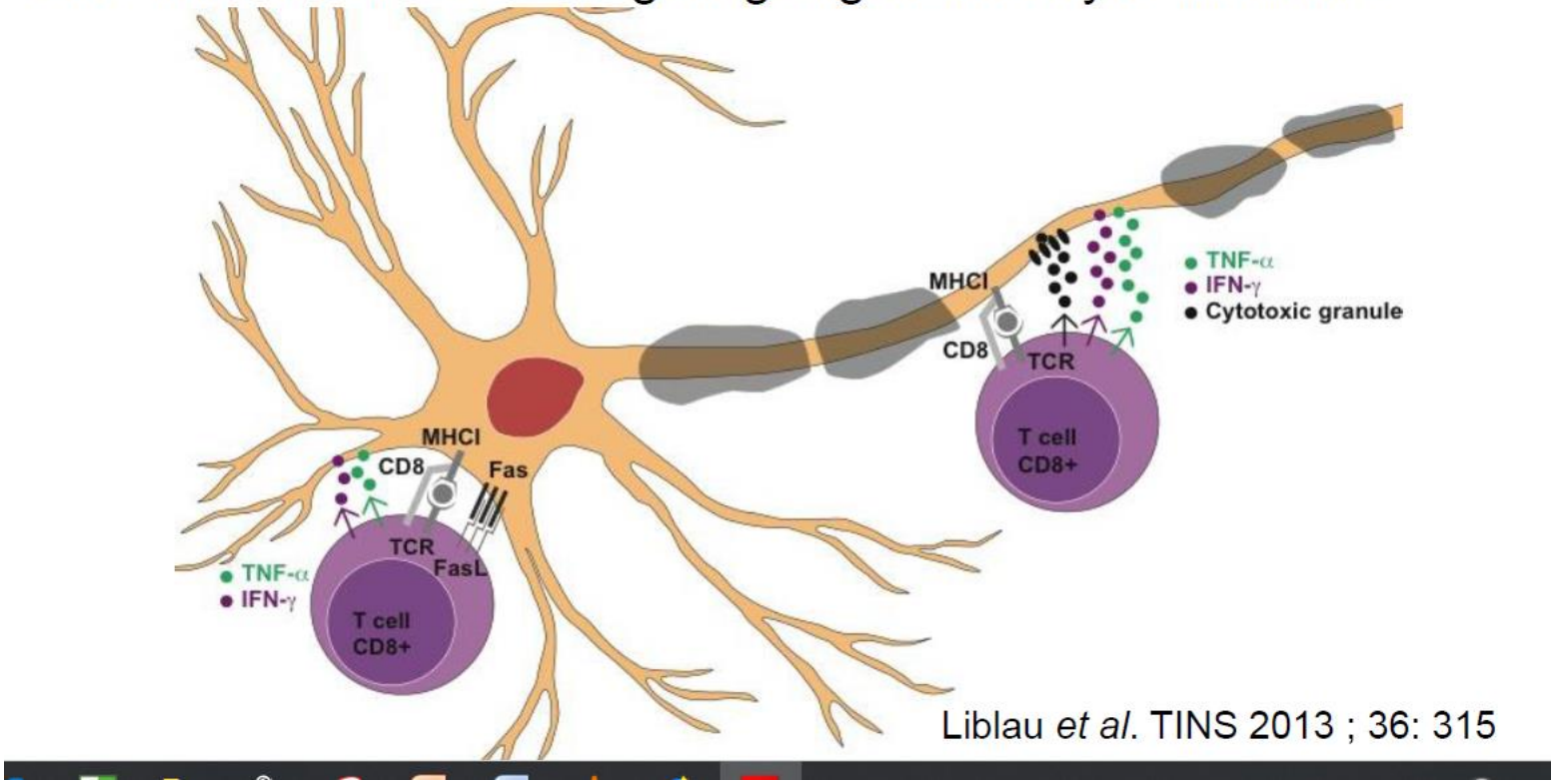


Non-phosphorylated neurofilaments

Collectively, these experiments indicate :

✓ That oligodendrocytes/neurons can process and present Ag to activated CD8 T cells and become their direct cellular targets.

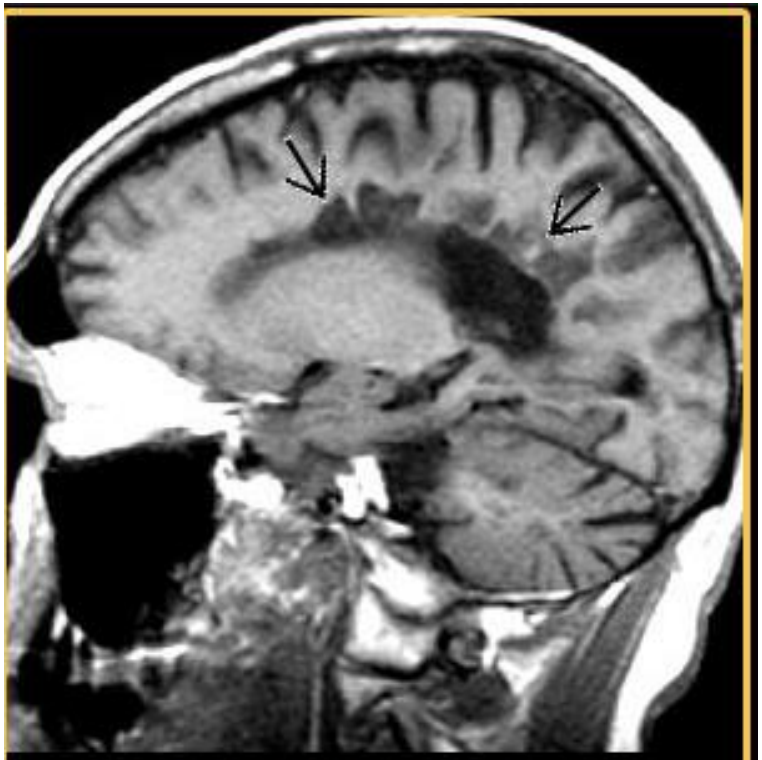
✓ That CD8 T cells can thereby contribute to tissue damage in CNS immune diseases targeting oligodendrocytes/neurons.



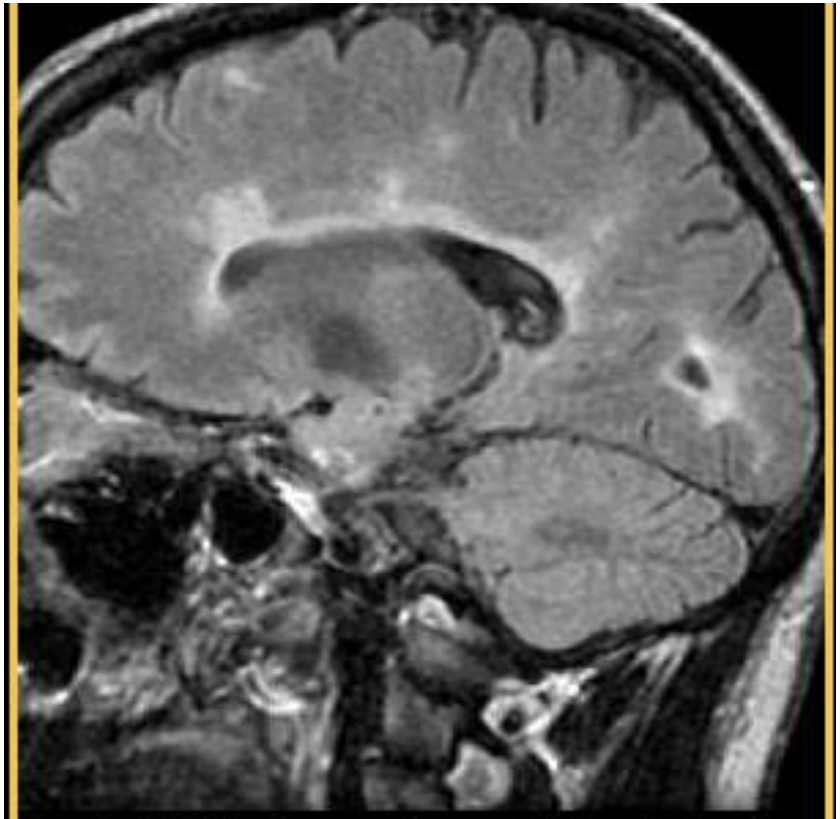
CD8Tcells recognise antigen peptides within MHC-I complex and release perforin ,cytotoxic granul

Cytotoxic activiy

- CD8 recognise Ag in Class-I
- CD4 may have cytolytic activity but recognise Ag within Class-II
- PERFORIN ,granzymes A and B,
- CRT[calreticulin],cathepsin
- Granule independed mechanism of target cell lysis associated wuth Fass lingand



Sagittal T1WI MR shows multiple hypointense lesions ("black holes") in the deep white matter (black arrow) related to axonal destruction. Note the associated moderate ventricular and sulcal enlargement.



Sagittal FLAIR shows callososeptal hyperintensities radiating from the lateral ventricles with a typical perpendicular orientation, characteristic of multiple sclerosis.

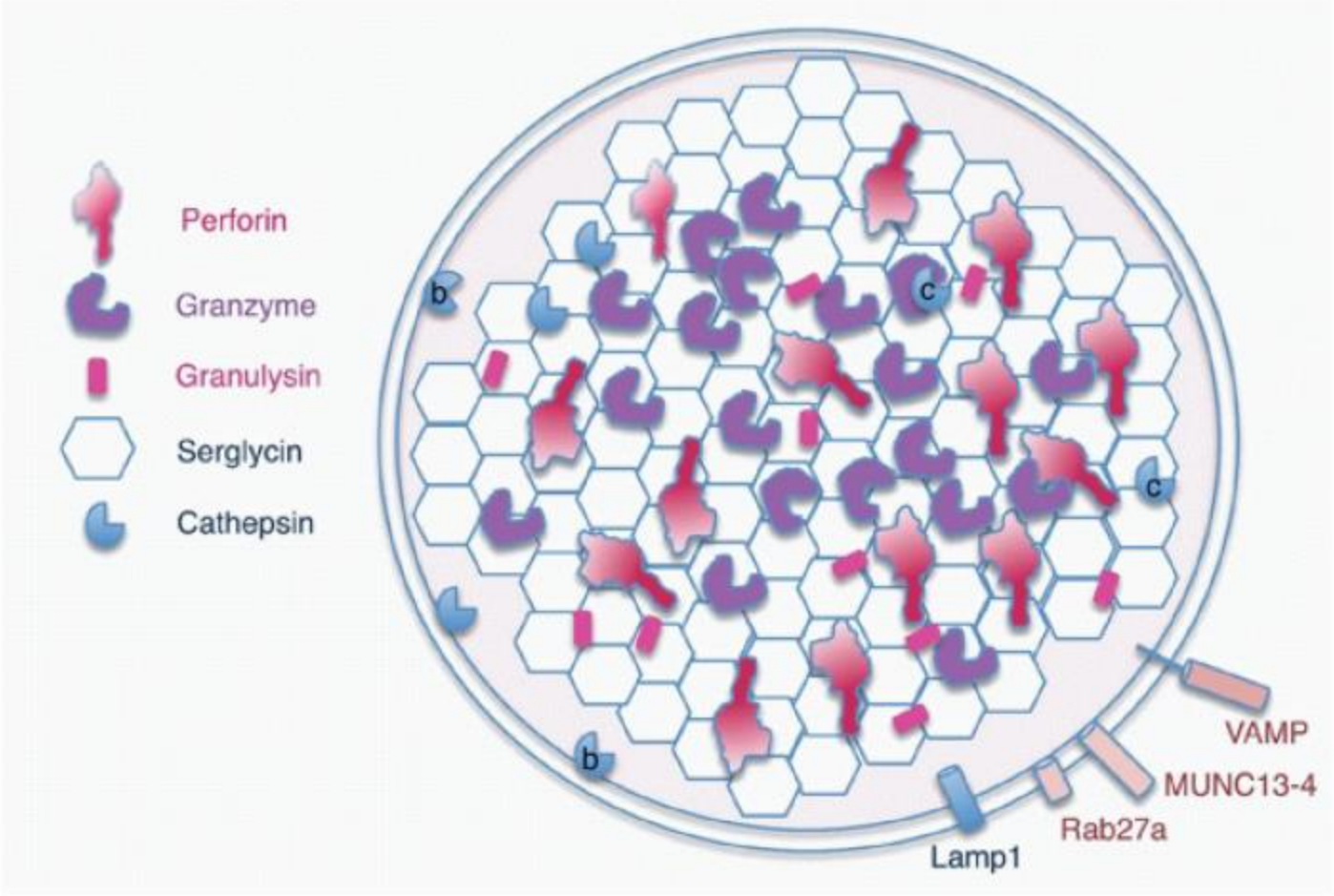


FIG. 37.2. Key Components of Cytotoxic Granules. The cytolytic effector molecules, perforin, granzymes, and granulysin, are bound to the serglycin proteoglycan. Cytotoxic granules also contain molecules found in all lysosomes, such as Lamp1 (CD107a) and

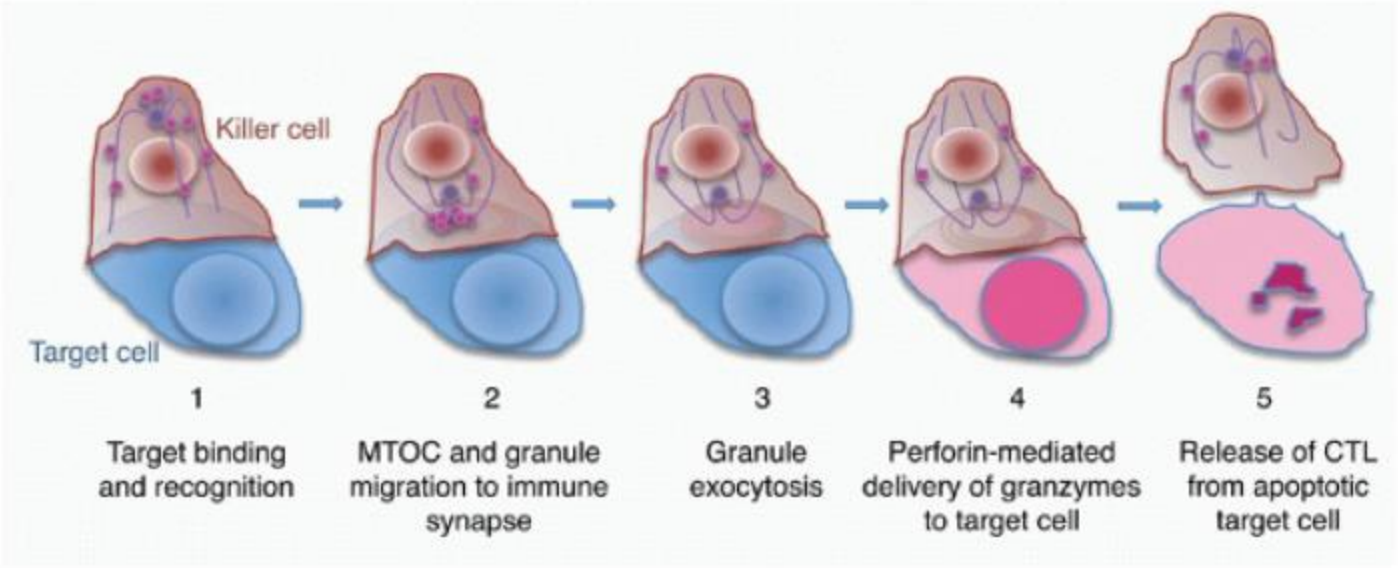


FIG. 37.3. Steps in Granule-Mediated Cytotoxicity. After the killer cell recognizes a target cell *(1)*, an immune synapse is formed at the interface and the microtubule organizing center (MTOC) moves to the synapse, reorganizing the microtubule network *(2)*. Cytotoxic granules move along microtubules to dock at the killer cell membrane in the central supramolecular activation complex (c-SMAC) of the immune synapse. Granule membranes fuse with the killer cell plasma membrane, releasing their contents *(magenta)* into the immune synapse *(3)*. Perforin delivers the granzymes into the cytosol of target cells **(*4*) where they initiate apoptotic death *(5)*. The granzymes concentrate in the nucleus of target cells. The killer cell then detaches from the dying cell and is free to seek out additional targets.**

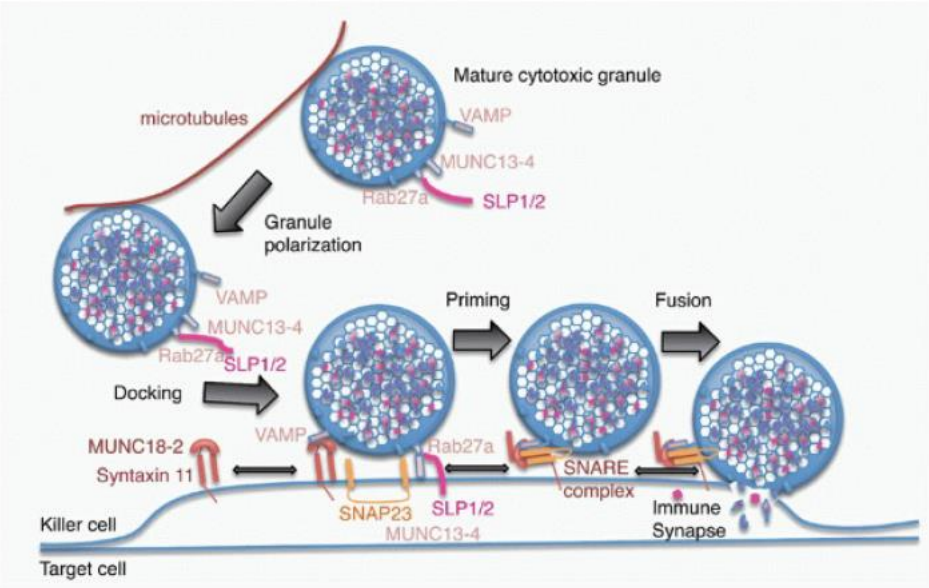


FIG. 37.4. Model of Granule Exocytosis. In response to antigen recognition, the mature cytotoxic granule moves along microtubules, probably with assistance from the actin-myosin cytoskeleton (*not shown*) to dock at the cell membrane at the immune synapse. A cytotoxic granule vesicle-associated soluble N-ethylmaleimide-sensitive factor accessory (SNARE) complex component (VAMP) protein binds to Munc18-2, which is associated with plasma membrane syntaxin 11. Cytotoxic granule proteins Rab27a and Munc13-4, in association with a synaptotagmin SLP1 or SLP2, help anchor the granule

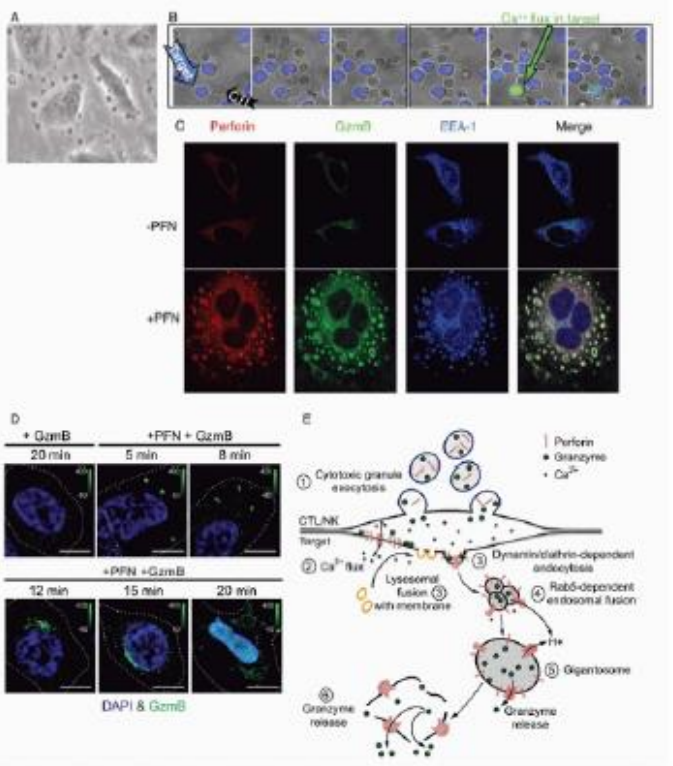


FIG 37.5. Current Model of Perforin Delivery of Granzymes into the Target Cell. **A:** Perforin treatment of HeLa cells causes dramatic membrane perturbation and blebbing. **B:** Killer cell degranulation causes a transient calcium influx in target cells that persists for a few minutes. In this experiment from Keefe et al.,[157] PHA-activated human cytotoxic T lymphocytes were incubated with Fura-2-loaded, anticluster of differentiation three-coated U937 cells, and images were obtained every 30 seconds. The Fura-2 indicator dye is *blue* when calcium is low and *green* when it is elevated. **C:** Perforin and granzyme B are endocytosed into giant EEA-1-staining endosomes (image courtesy of Jerome Thiery). **D:** When HeLa cells are treated with perforin and granzyme B, within 5 minutes, granzyme B (*green*) concentrates in gigantosomes and is released beginning after about 12 minutes. The released granzyme concentrates in the target cell nucleus. **E:** Model for perforin delivery. After cytotoxic granule exocytosis into the immunologic synapse *(1)*, perforin multimerizes in the target cell membrane to form small transient pores through which calcium enters *(2)*, triggering a plasma membrane repair response *(3)* in which lysosomes fuse with the damaged plasma membrane and perforin and granzymes are rapidly internalized by endocytosis. Perforin and granzyme-containing endosomes then fuse in response to the transient calcium flux *(4)* to form gigantosomes. Within gigantosomes, perforin continues to multimerize to form larger pores, preventing

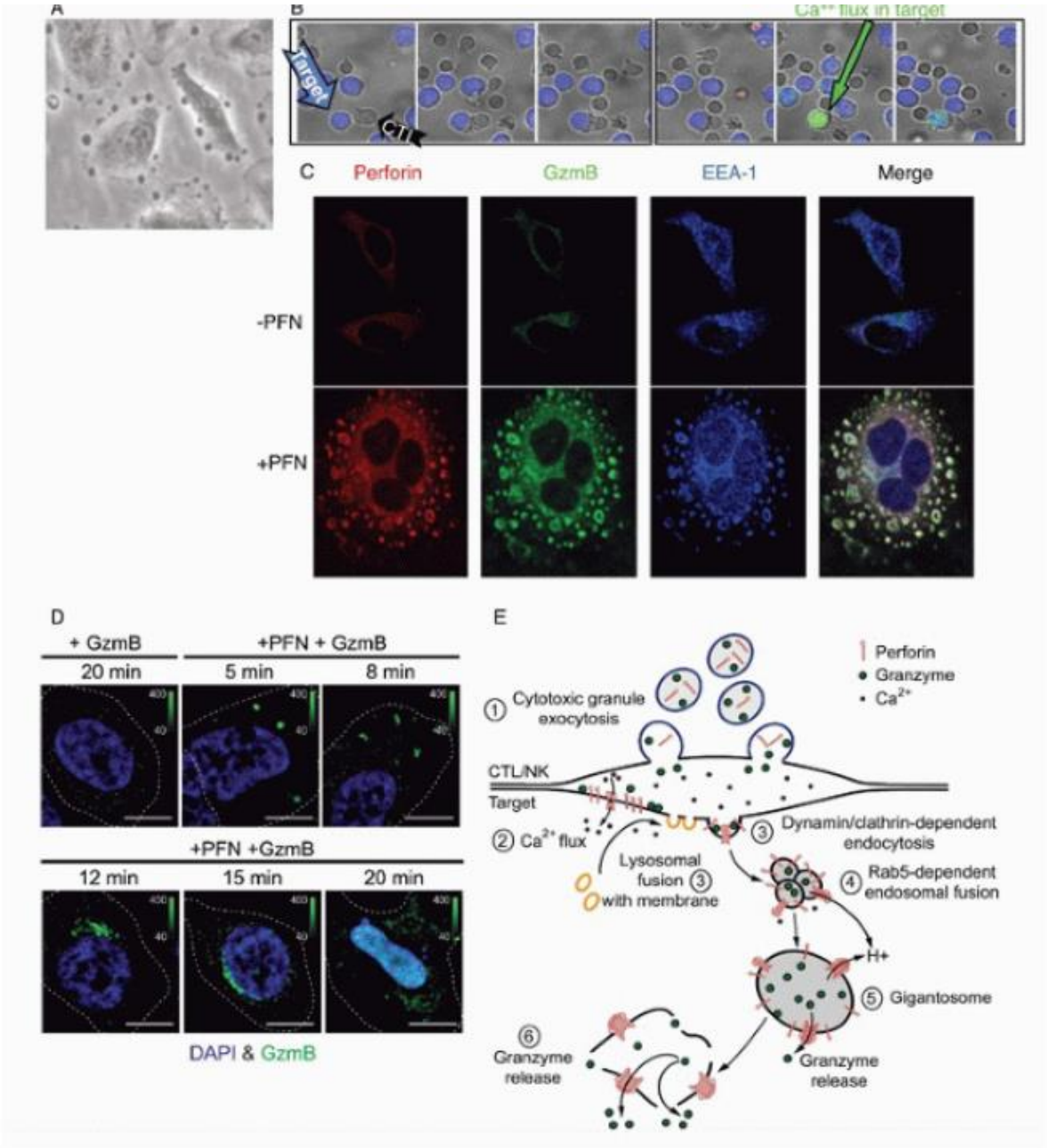


FIG 37.5. Current Model of Perforin Delivery of Granzymes into the Target Ce

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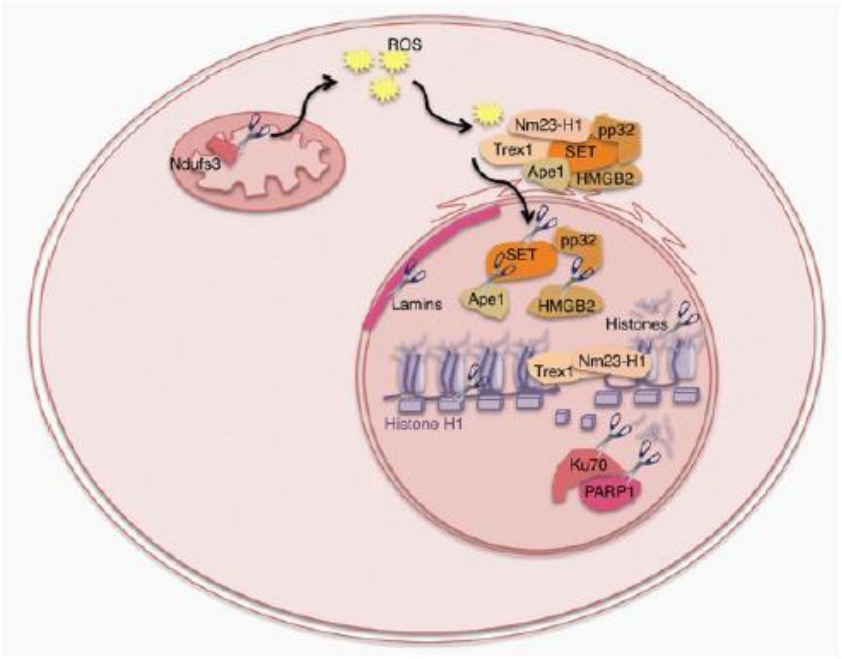


FIG 37.6. The Granzyme A Pathway of Cell Death. Reactive oxygen species generated by granzyme A (represented by *scissors*) cleavage of Ndufs3 in electron transport complex I in mitochondria drives the endoplasmic reticulum-associated SET complex into the nucleus. Granzyme A enters the nucleus by an unknown pathway. In the nucleus, Granzyme A cleaves three components of the SET complex (SET, HMGB2, and Ape1) to activate two nucleases in the complex to make single-stranded deoxyribonucleic acid (DNA) lesions; NM23-H1 makes a nick, which is extended by the exonuclease Trex1. Granzyme A also degrades the lamins and the linker histone H1 and removes the tails from the core histones, opening up chromatin and making it more accessible to these nucleases. DNA repair proteins Ku70 and PARP-1 are also targets.

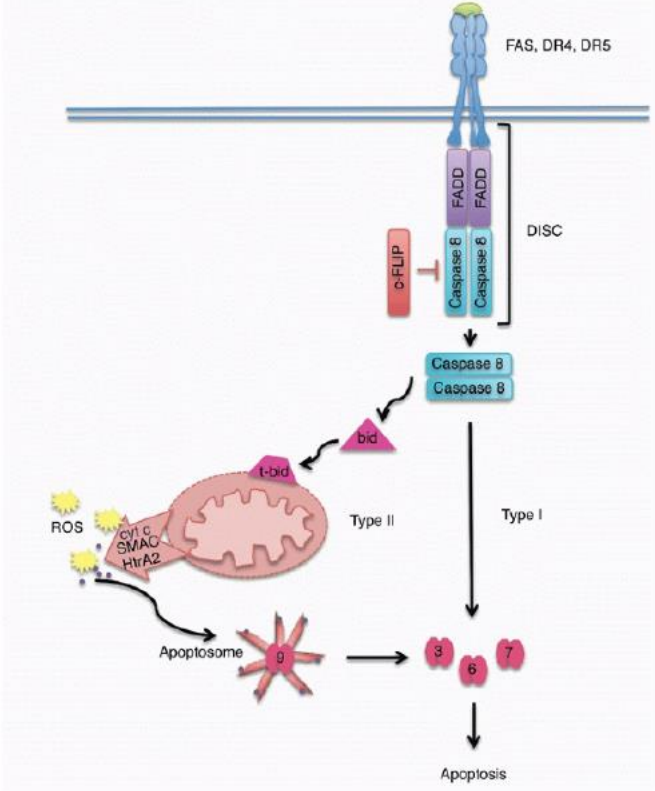
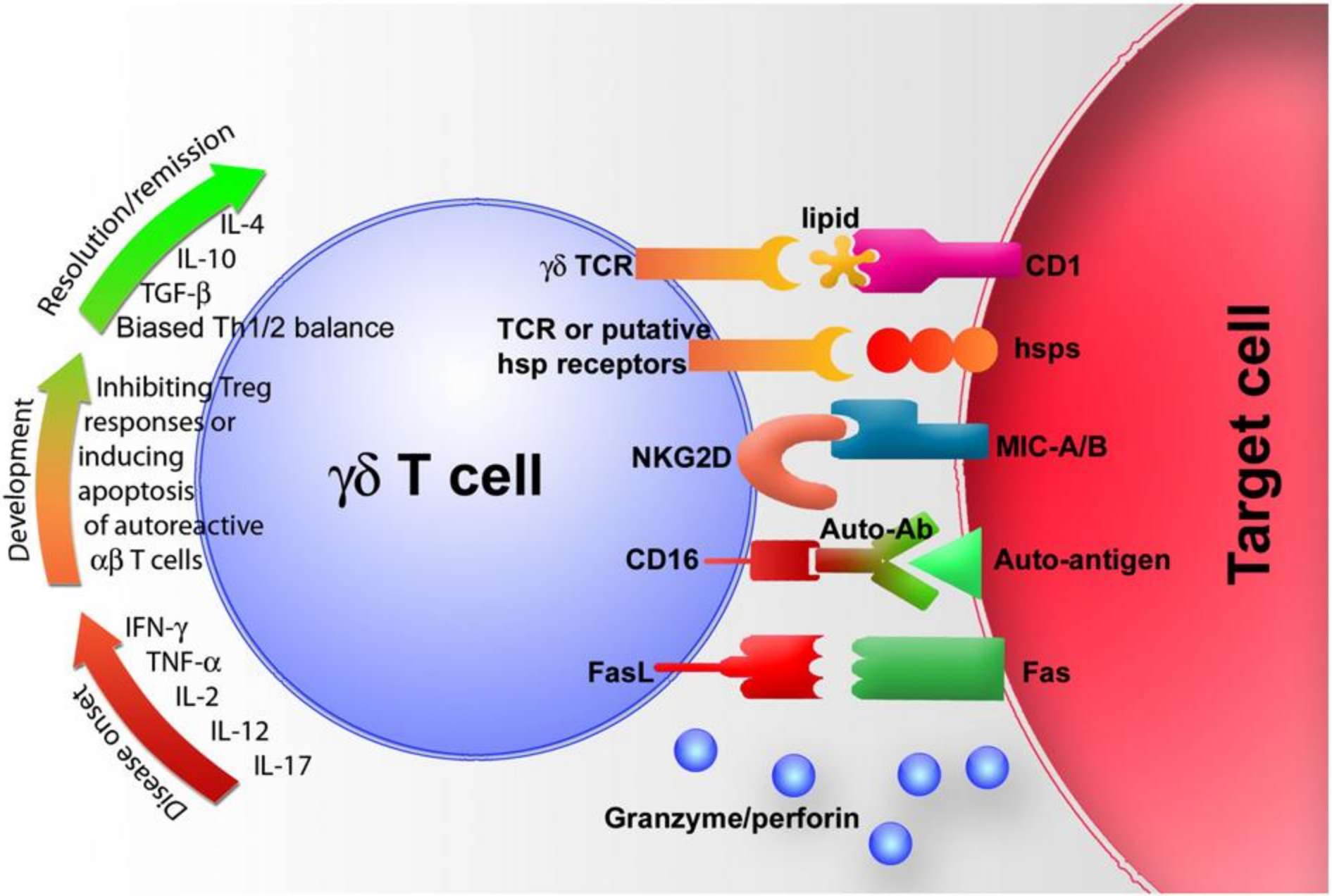


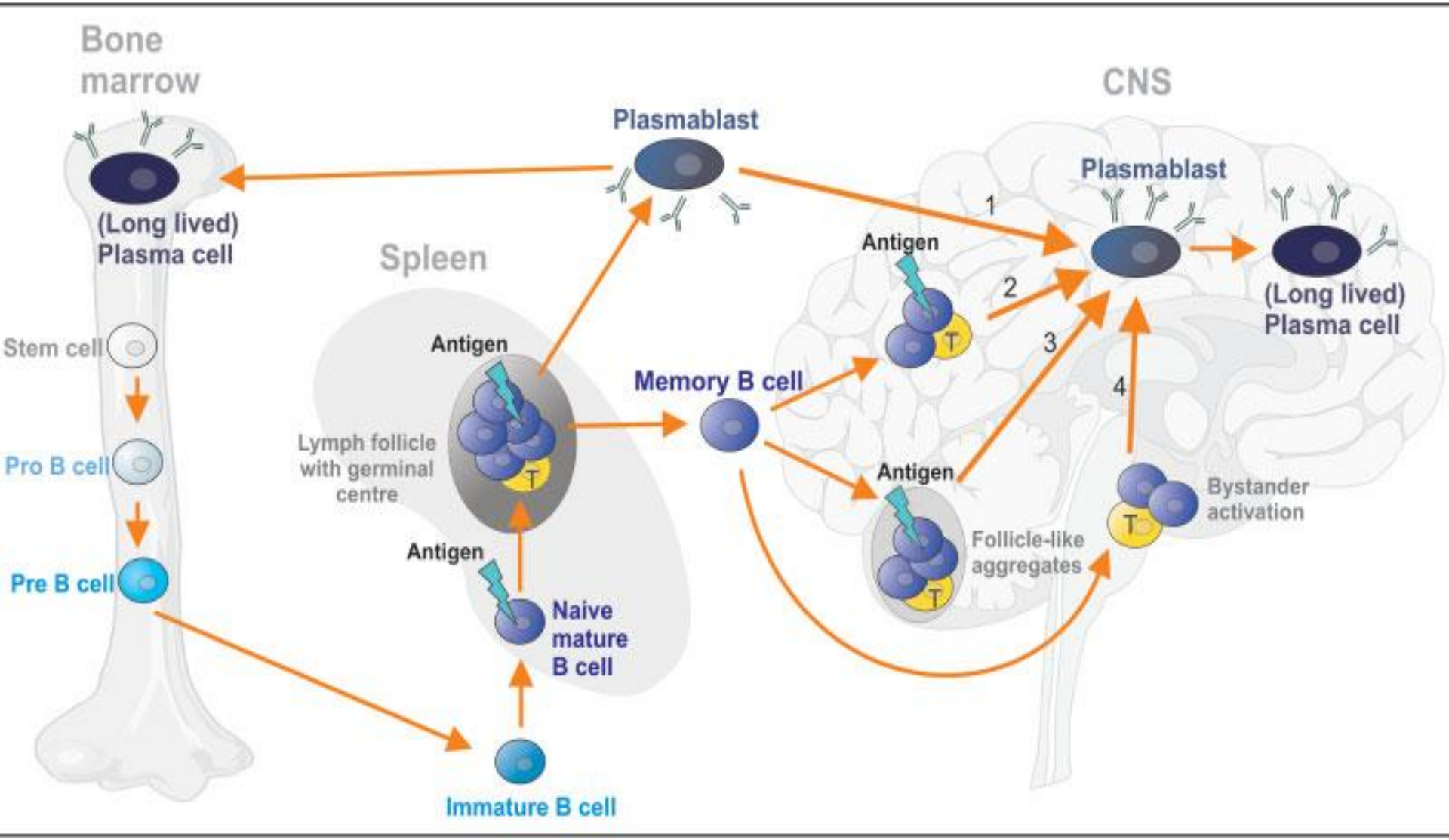
FIG. 37.8. Death Receptor Pathways of Apoptosis. Ligation of a death receptor trimer on target cells recruits the deathinduced signaling complex, which activates caspase-8, releasing it to the cytoplasm where it can cleave Bid to activate mitochondrial apoptotic pathways and cleave and activate the effector caspases-3, -6, and -7. In type I cells, apoptosis does not require mitochondrial amplification, whereas type II cells die only if mitochondrial mediators of apoptosis are released. The caspases activated downstream of caspase-8 are represented by numbered dimers. Cytochrome c required for caspase-9 activation in the apoptosome is represented by a *blue ball*. Caspase-8 activated by death receptor signaling and granzyme B-mediated death are very similar, although the granzyme B-mediated death is much more rapid. Fas-associated death domain can also recruit an alternate signaling complex that leads to cell activation rather than apoptosis

Cytotoxic activiy

- CD8 recognise Ag in Class-I
- CD4 may have cytolytic activity but recognise Ag within Class-II
- PERFORIN ,granzymes A and B,
- CRT[calreticulin],cathepsin
- Granule independed mechanism of target cell lysis associated wuth Fass lingand

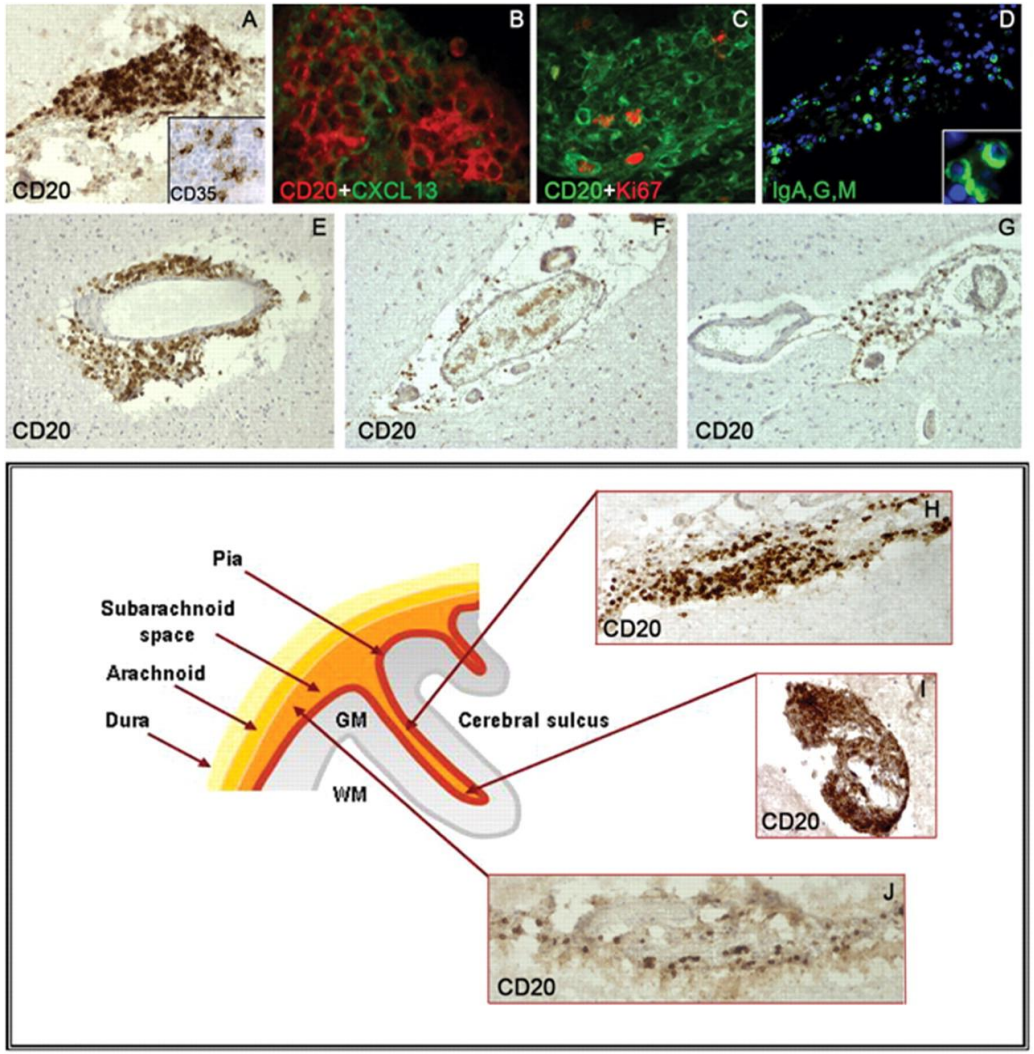


Z Chen and M Freedman 2010



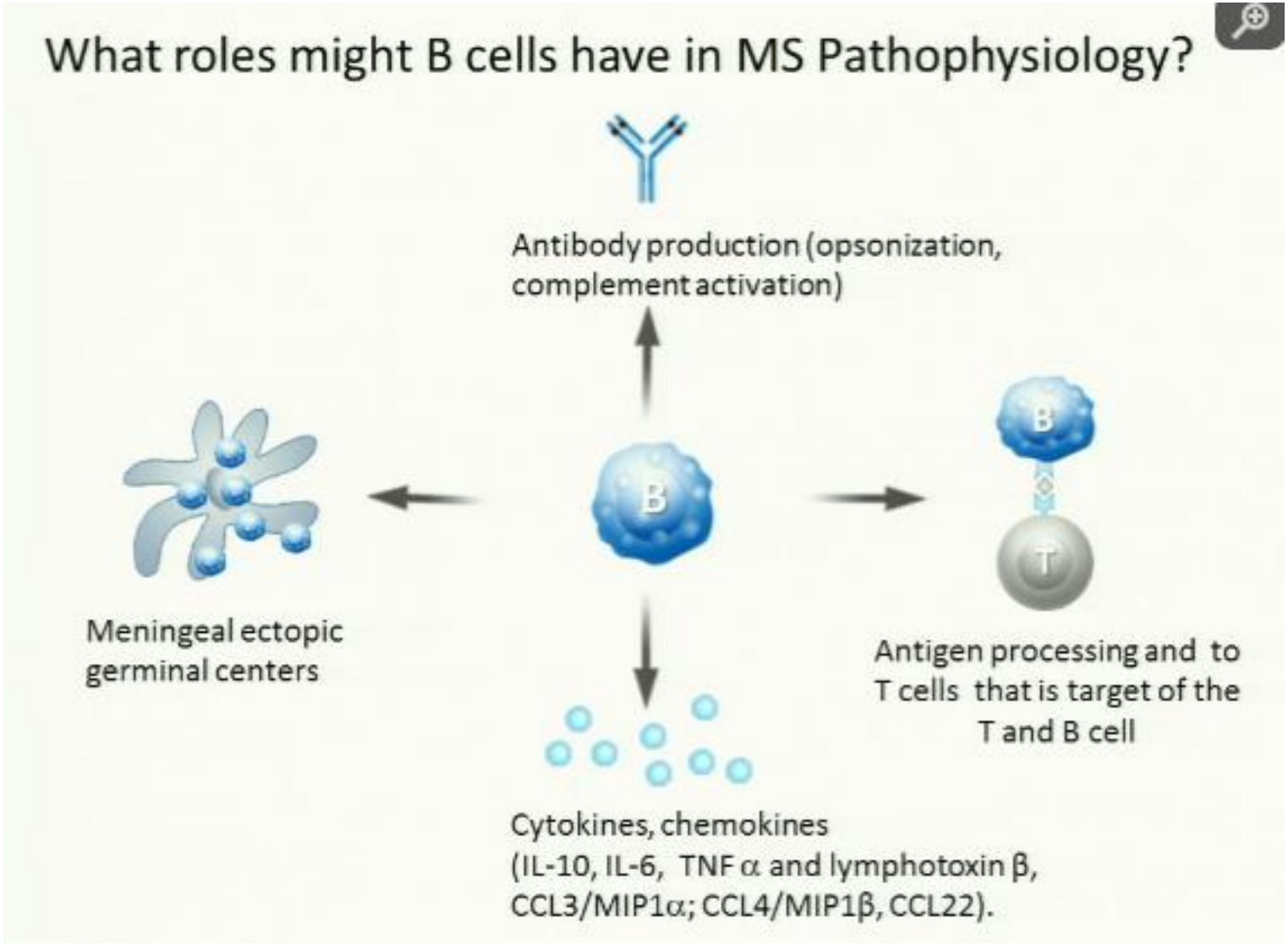
Meinl et al2006

Characterization of ectopic B-cell follicles and inflammatory cell infiltrates in post-mortem brain tissue from cases with SPMS and PPMS



Magliozzi, R. et al. Brain 2007 130:1089-1104; doi:10.1093/brain/awm038

BRAIN A JOURNAL OF NEUROLOGY


What roles might B cells have in MS Pathophysiology?
Antibody production (opsonization, complement activation)
B
Meningeal ectopic germinal centers
B
T
Antigen processing and to T cells that is target of the T and B cell
Cytokines, chemokines
(IL-10, IL-6, TNF α and lymphotoxin β, CCL3/MIP1α; CCL4/MIP1β, CCL22).

CrossA 2013

Polymyositis

- CD8 mediated Class-I restricted
- Lymphocyte infiltration within muscle parenchyma

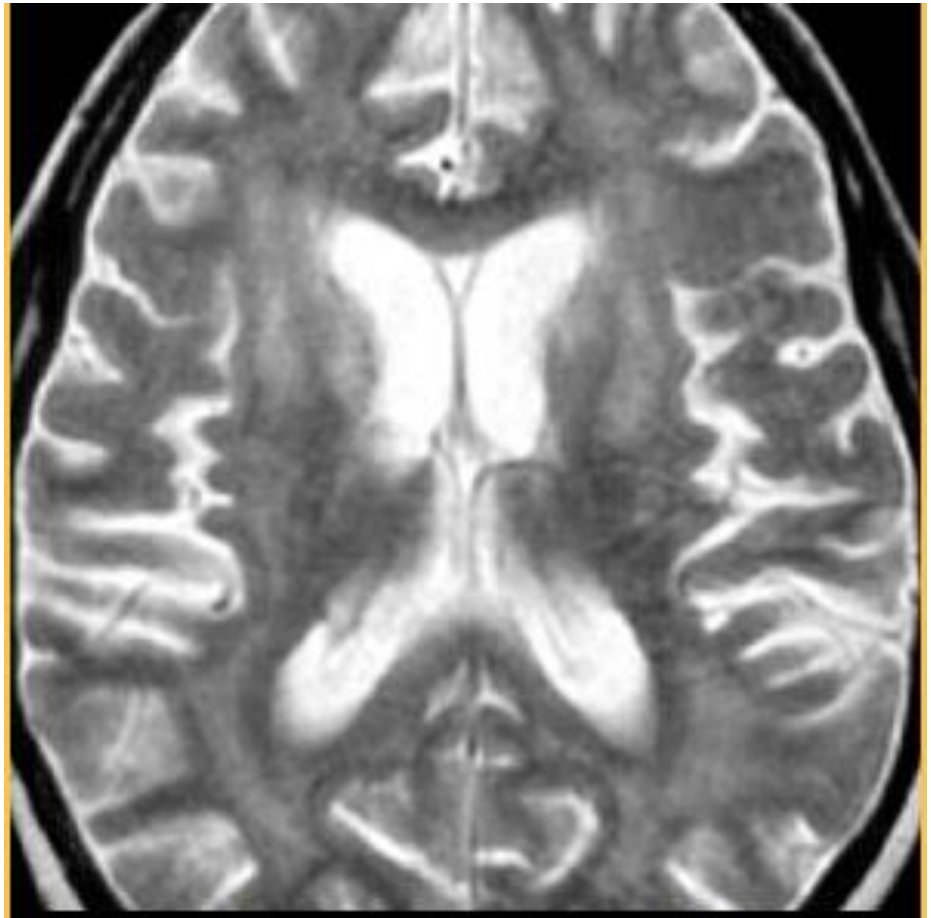
- Post infectious E/M
- Post vacination E/M

Absence or diminished immune action

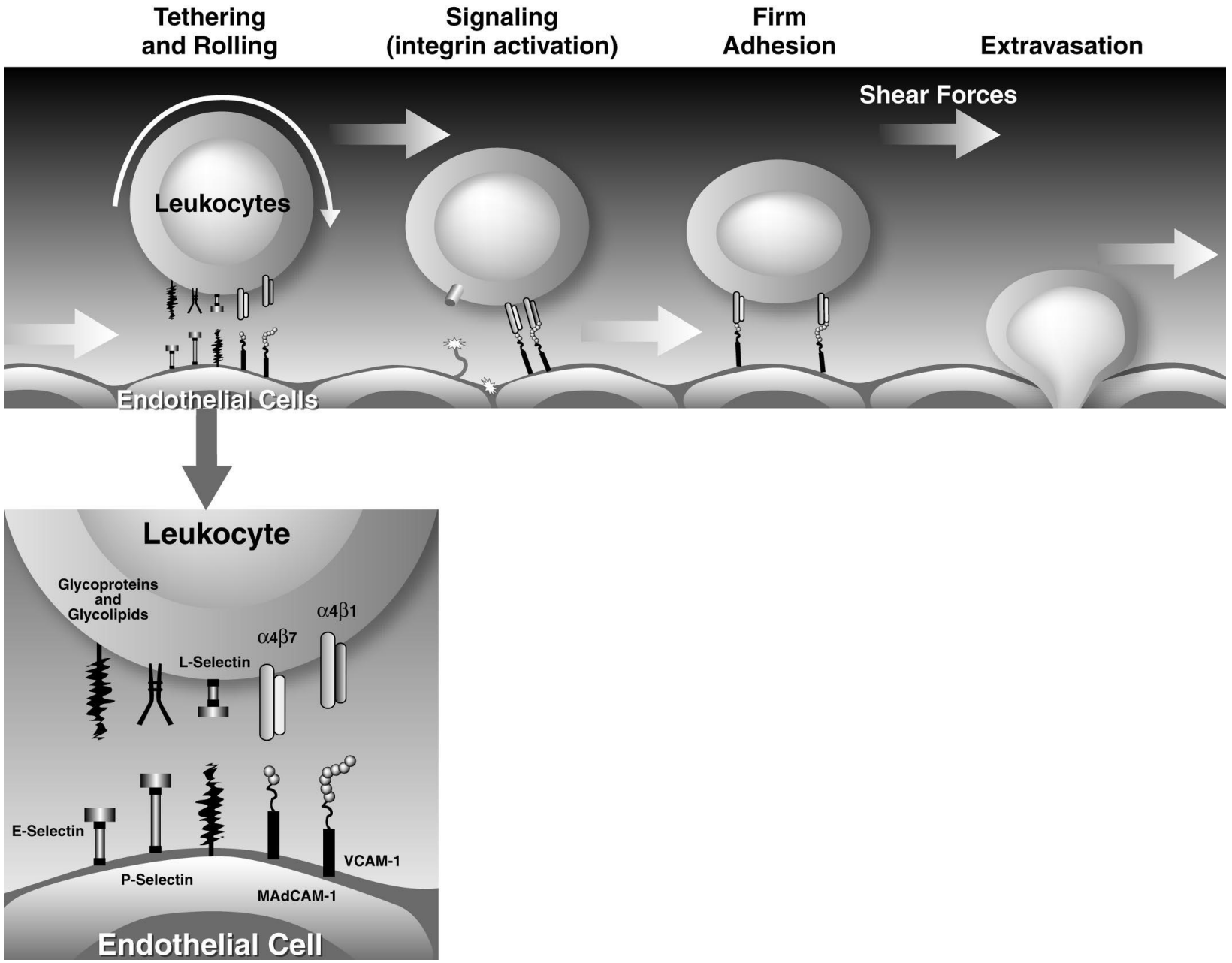
- PML
- AIDS and CNS
- SSPE

HIV και Νευρικο συστημα

- Εγκεφαλοπαθεια: ανοια [πρωτοπαθης], ευκαιριακες λοιμωξεις, λεμφωμα ΚΝΣ
- Μυελοπαθεια :κενοτοπιωδης εκφυλισις
- Αισθητικη αξονικη νευροπαθεια [ραχιαια γαγγλια sulfatide]



Axial T2WI in the same patient shows diffuse, symmetric periventricular white matter hyperintense signal abnormality, highly suggestive of HIV encephalopathy (HIVE). This symmetrical pattern would not be expected in progressive multifocal leukoencephalopathy, another white matter disease that affects HIV-positive patients.



Hartung 2006

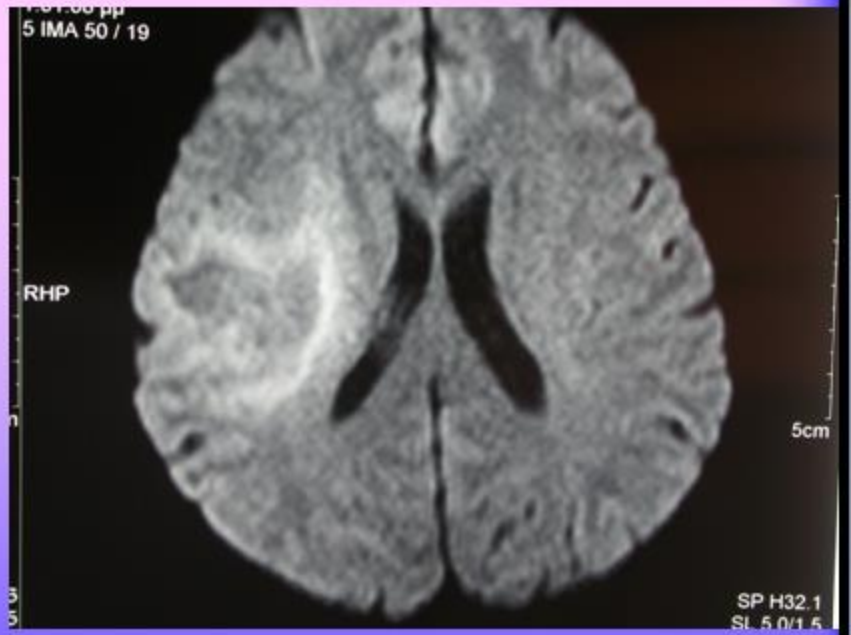
PML Clinical Expression

- Presenting symtom combinational of cognitive and behavoral changes[54%]
- Motor weakness [42.5%]
- Visual impairment [40.5%]
- EDSS increase[4.1+-0.3 to5.4+-0.3]

PML-MT

DWI: 3 ζώνες

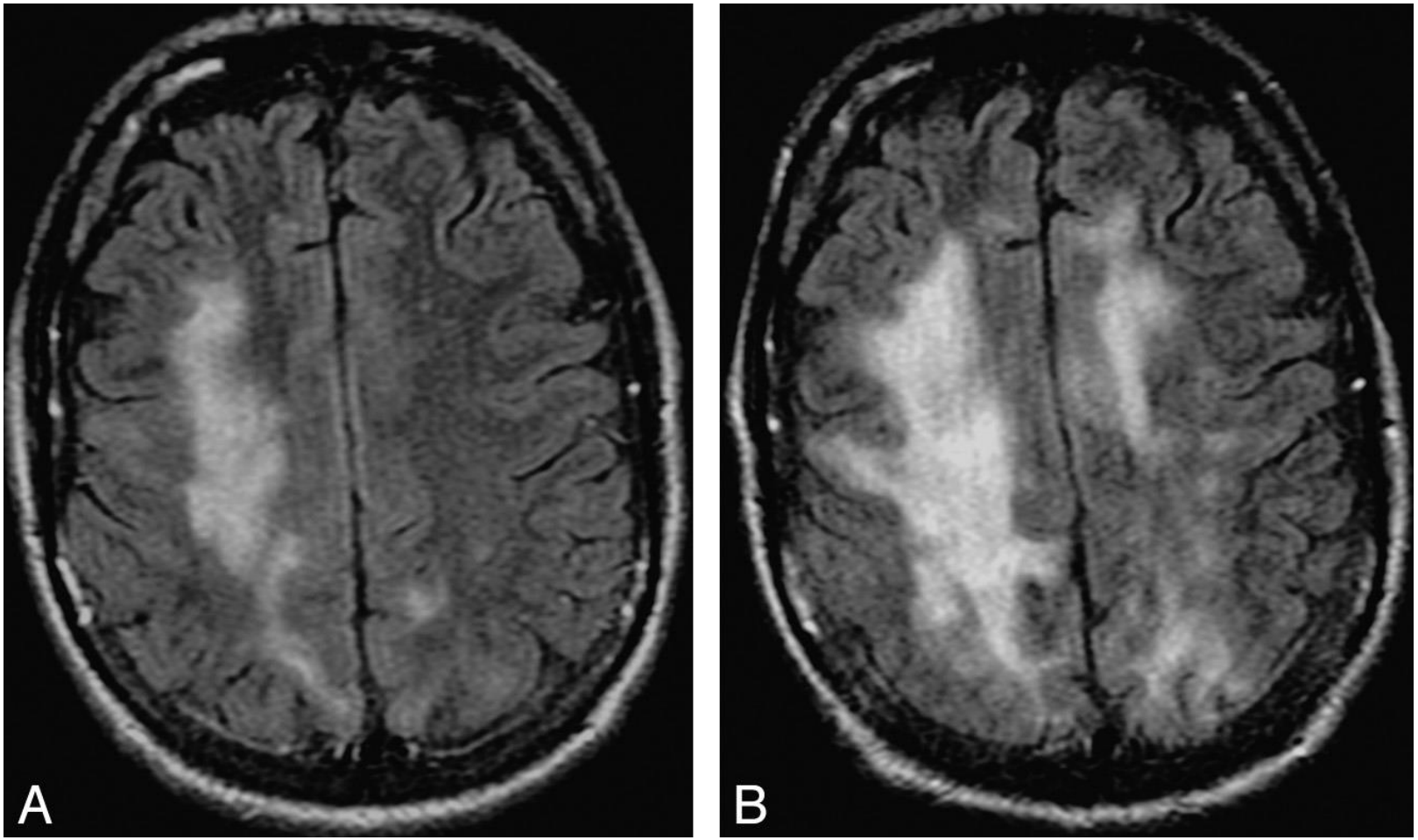
- Κεντρική ζώνη: νέκρωση
- Οίδημα αγγειογενές
- Περιφερικός δακτύλιος: κυτταροτοξικό οίδημα κυτταρικός θάνατος, επέκταση βλαβών.

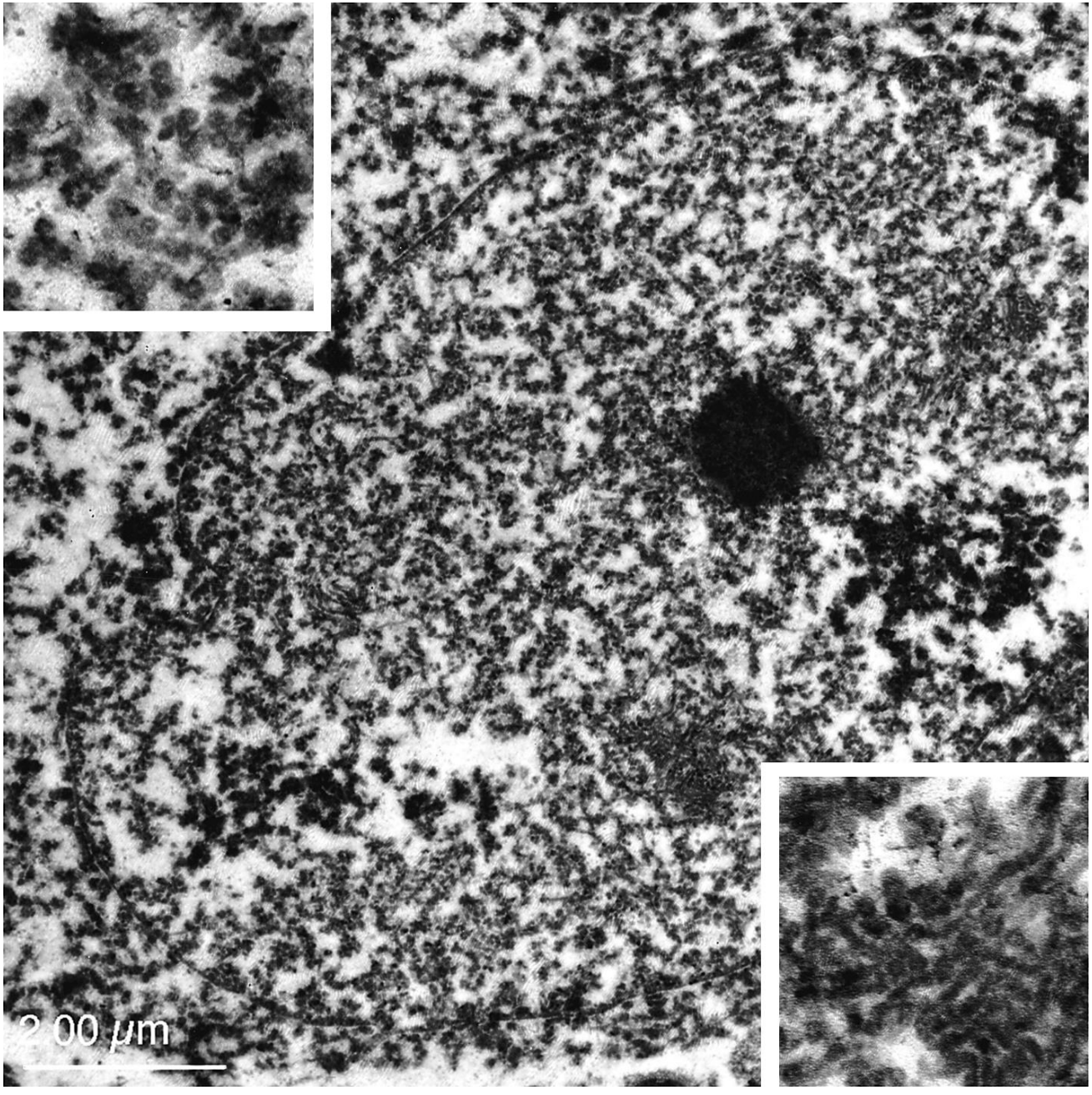


PML diagnosis

- Increased T2 abnormalities,subcortical ,tend to involve U fibers, little contrast enhacement . Occipital lessions more than frontal.
- CSFmild increase of protein up to 100mg/DL.pleocytosis less than 25 cells /mm3.
- CSF PCR is specific for significant PML pathology .Sensitivity in general 76%[low abudance of virus in CSF,storage and handling conditions,inhibitors in CSF ,small volume]

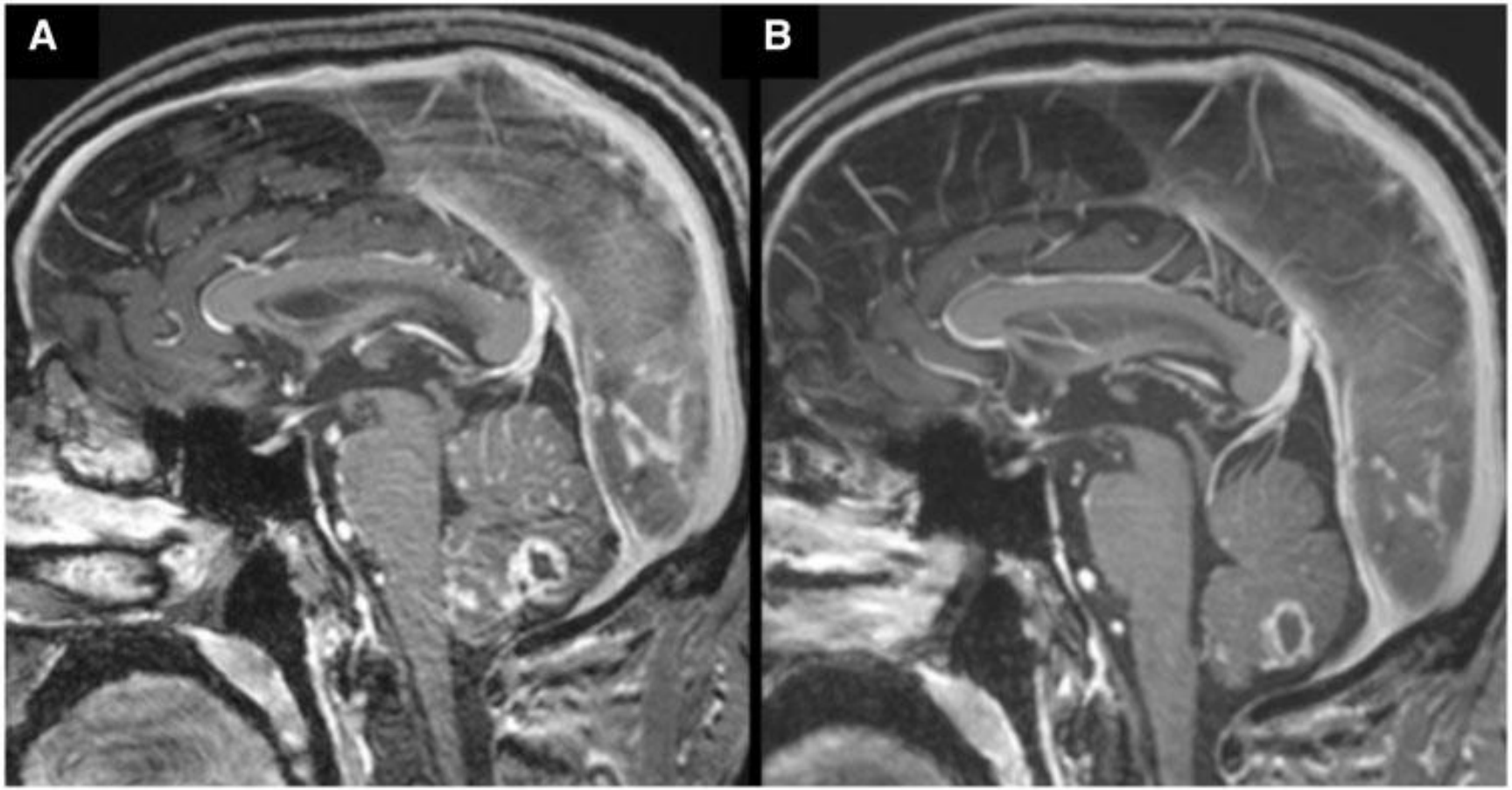
PML evolution




2.00 μm

IRIS key points

- T-cell mediated encephalitis with high morbidity and mortality rate
- Oportunistic infection
- Restoration of immune function should be with caution
- Combination of CNS -penetration antibiotics with prolonged steroids are needed to treat the syndrome



A case of paradoxical IRIS .Cryptococus ,johnson et al2011

SSPE

- Αυστηρα ενδοκυτταριος λοιμωξις αποτον ιο ιλαρας
- Ο ιος μεταδιδεται από κυτταρο σε κυτταρο με πινοκυττωση

iris

cjd