Medora

La community dei professionisti della salute By Roche

M-IT-00001113

Introduction to MS

Introduction to MS

1. Definition
2. Exploring the role of the immune system in the neuropathology of MS

Disclaimer

Il presente materiale, di carattere meramente informativo e non promozionale, viene reso disponibile per approfondimento ai professionisti sanitari

1

Definition

Definition of MS:

MS is a chronic, immune-mediated disease of the CNS characterised by inflammation, demyelination and degenerative changes, leading to neurological symptoms and accumulating disability:[1,2]

CNS, central nervous system.

1. Montalban X. et al. Mult Scler. 2018;24:96–120;
2. Practice guideline: Disease-modifying therapies for adults with multiple sclerosis. https://www.aan.com/Guidelines/home/GetGuidelineContent/904. Accessed January 2020.

MS is a chronic, neuroinflammatory, neurodegenerative disease of the CNS

MS was first defined clinically in 1868 by Jean-Martin Charcot, the “Father of Neurology”, who described cadavers showing signs of la sclérose en plaques – scarring of the nerves [1]

- Charcot was the first person to diagnose MS in a living patient and developed a crude diagnostic triad: [1]

1. **Nystagmus** (involuntary, rapid movements of the eyes)[2]
2. **Intention tremor** (tremor occurring during target-directed movement)[3]
3. **Scanning speech** (excess and equal stress on syllables during speech)[4]

- While these symptoms are not necessarily diagnostic by modern standards, they do provide a basic outline of the most common symptoms of MS1

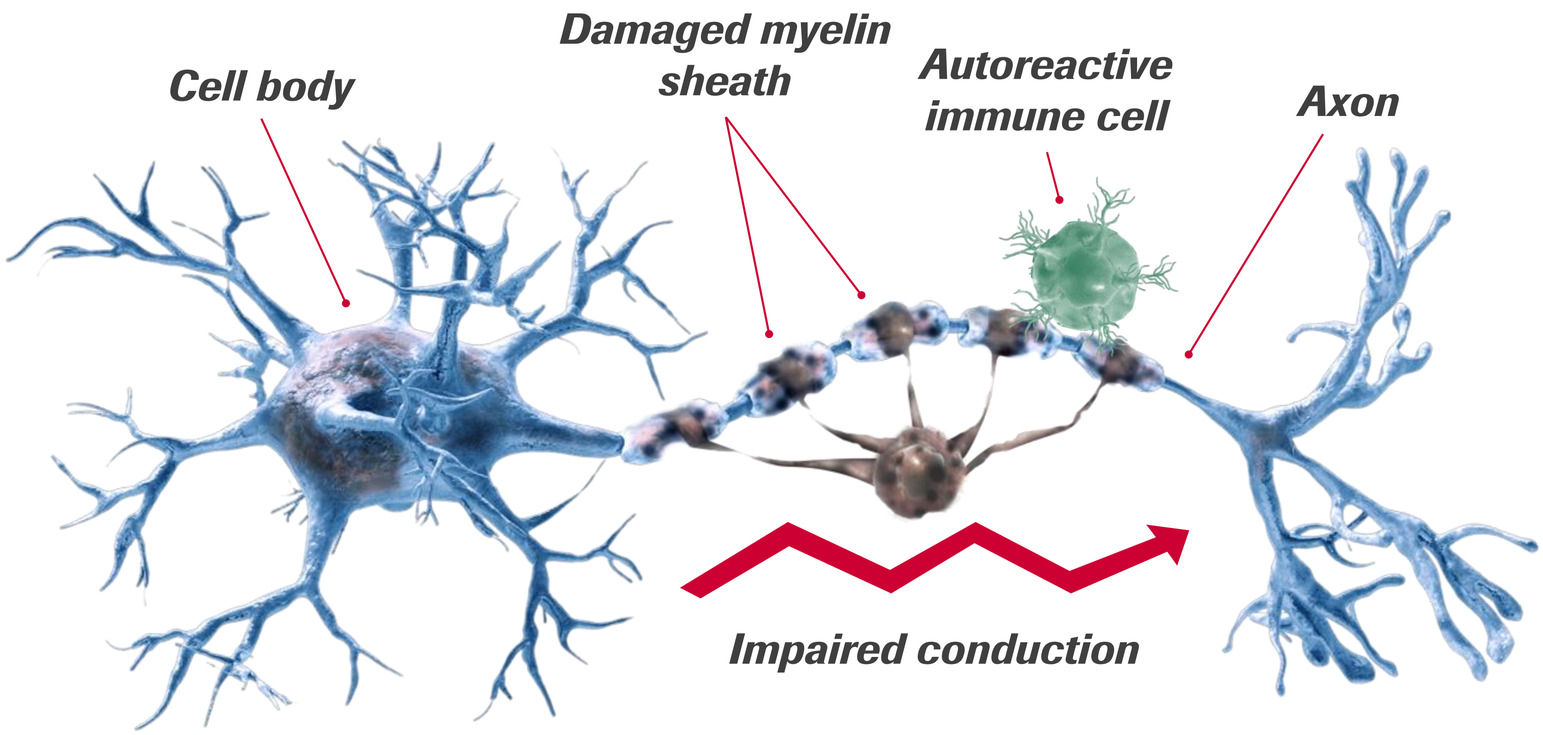
Jean-Martin Charcot[1]

CNS, central nervous system.

1. Kumar DR, et al. Clin Med Res. 2011;9:46–9; 2. Serra A, et al. Front Neurol. 2018;9:31; 3. Koch M, et al. J Neurol. 2007;254:133–45;
4. Hartelius L, Nord L. Folia Phoniatr Logop. 2000;52:228–38

MS is driven by an immune-mediated, inflammatory response

Demyelinated neurone resulting in impaired conduction:[1]



MS is characterised by the destruction of the conductive myelin sheath* by inflammatory autoreactive immune cells. This results in the accumulation of lesions, reduced conductivity of nervous electrical signals and significant, irreversible, axon damage[1]

*The myelin sheath is an electrically insulating layer of lipids and proteins that allows CNS nerves to increase conduction velocity2

Bruck W. J Neurol 2005;252:v3–v9; 2. Stassart RM, et al. Front Neurosci 2018;12:467.

MS is characterised by both acute and chronic disease activity, manifesting as relapses and long-term disability progression

MS is the most common non-traumatic cause of neurological disability in young adults[1,2]

Acute and chronic disease activity is common in the absence of clinical symptoms[3,4]

Once a threshold of irreversible disability has been reached, it may be too late for patients to benefit from treatment[2,5–8]

Treating earlier may reverse some aspects of early dysfunction[2,9]

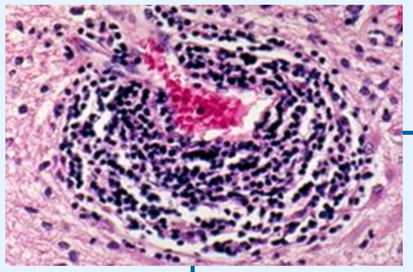
1. Conway D, Cohen JA. Lancet Neurol 2010;9:299–308; 2. Compston A, Coles A. Lancet 2002;359:1221–31; 3. Miller DH, et al. Mult Scler 2008;14:1157–74;
4. Río J, et al. Nat Rev Neurol 2009;5:553–60; 5. Confavreux C, et al. N Engl J Med 2000;343:1430–8; 6. Leray E, et al. Brain 2010;133:1900–13;
7. Coles AJ, et al. Ann Neurol 1999;46:296–304; 8. Coles AJ, et al. J Neurol 2006;253:98–108; 9. Narayanan S, et al. J Neurol 2001;248:979–86.

Neuropathology of MS

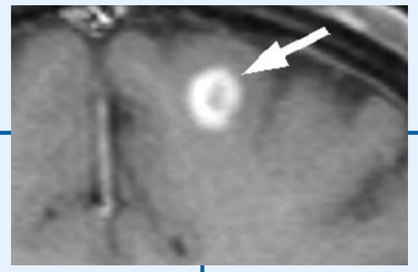
Quiz answers

Pathological mechanisms driving focal white matter injury in MS

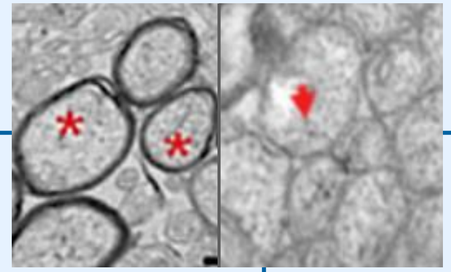
Inflammation



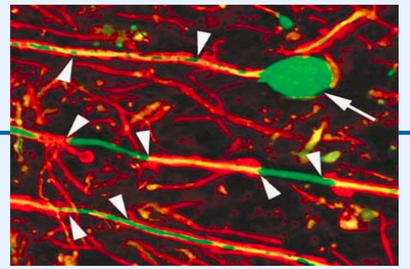
BBB disruption



Demyelination



Axonal damage



Clinical outcomes

- CNS atrophy
- Clinical progression
- Acute relapse

BBB, blood–brain barrier; CNS, central nervous system.

1. Filippi M, et al. Handbook of Clinical Neurology 2014;122:115–49; 2. Giovannoni G, et al. Mult Scler Relat Disord 2016;9:S5–48;
3. Bermel RA, Bakshi R. Lancet Neurol 2006;5:158–70; 4. Trapp BD, et al. N Engl J Med 1998;338:278–85.

The neuropathology of MS is the result of a complex interplay of acute and chronic mechanisms that vary over time

Acute inflammation

- BBB disturbance
- New waves of lymphocytes entering the CNS
- Adaptive and innate immune drivers of injury
- New classical active lesions

Chronic/trapped inflammation

- Slow expansion of pre-existing lesions
- Chronic activation of microglia
- Meningeal inflammatory aggregates
- Diffuse white matter injury and brain atrophy

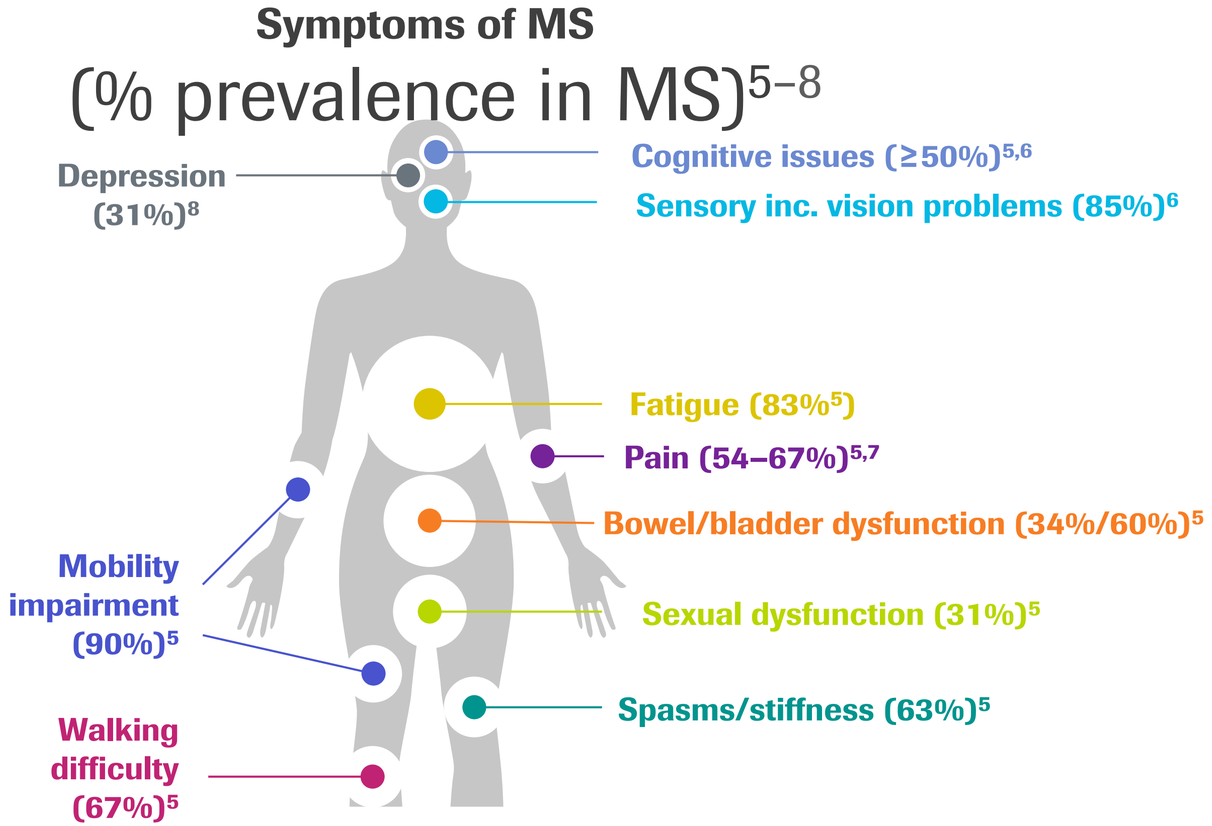
We still don’t have a full picture of MS neuropathology, but increasingly we see evidence of chronic inflammation in both RMS and PMS

BBB, blood–brain barrier; CNS, central nervous system; RRMS, relapsing-remitting MS.
Adapted from Lassmann H, et al. Nat Rev Neurol 2012;8:647–56.

MS relapses are variable, unpredictable and highly disruptive for patients

A relapse presents clinically as an episode of neurological disturbance in the absence of fever or infection, that lasts for at least 24 hours[1,2]

- **The relatively sudden onset of neurological symptoms may be functionally and socially incapacitating[3,4]**
- **A relapse evolves over a few days, plateaus, then remits over a few weeks or months[4]**
- **Relapses may be followed by periods of recovery and be spread over time, or they may occur without full recovery[1]**



The most common symptoms of MS include fatigue, impaired mobility and sensory disturbances,[5,6] but loss of normal neuronal function throughout the CNS can also lead to seizures, sexual dysfunction and speech problems[5]

CNS, central nervous system.

1. Thompson AJ, et al. Lancet Neurol 2018;17:162–73; 2. Poser CM, et al. Ann Neurol 1983;13:227–31; 3. Vollmer T. J Neurol Sci 2007;256:S5–13;
4. Leary SM, et al. Postgrad Med J 2005;81:302–8. 5. Zwibel HL. Adv Ther 2009;26:1043–57; 6. Kister I, et al. Int J MS Care 2013;15:146–58;
7. Rae–Grant AD, et al. Mult Scler 1999:5:179–83; 8. Boeschoten RE, et al. J Neurol Sci. 2017;372:331–41.

2

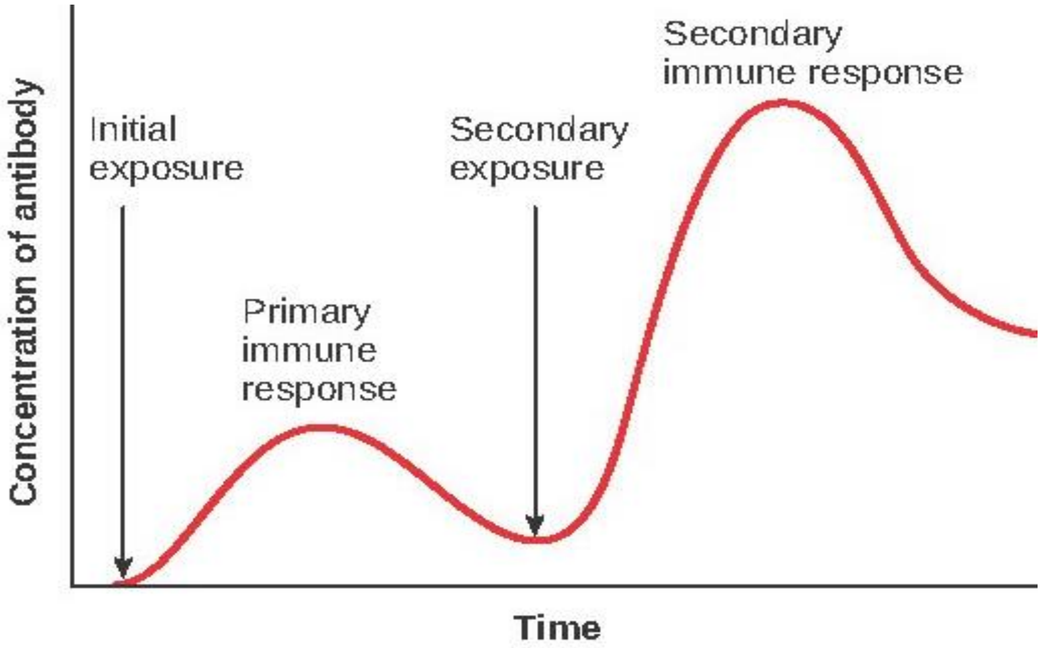
Exploring the role of the immune system in the neuropathology of MS

Overview of a typical immune response to pathogens

Innate immunity | **Adaptive immunity**

Innate response → **Antigen presentation** → **Adaptive response** → **Response resolution**

The immune response follows a typical path over time in response to pathogens



*Core of chronic active lesion.

1. Honmou O, *et al. J Neurosci*.1996;16:3199-208; 2. Kuhlmann T, *et al. Brain* 2002;125:2202–12; 3. De Stefano N, *et al*. *Arch Neurol* 2001;58:65–70.

Overview of a typical immune response to pathogens

Innate immunity

Adaptive immunity

Innate response

A fast, non-specific defence against pathogens (disease-causing microorganisms), comprised of first responder cells and proteins. Typically involves inflammation, pathogen killing and cell recruitment[1].

Antigen presentation

This is the link between the innate and adaptive immune responses. After innate response cells contact invader, or “antigen”, the antigen is presented to the cells of the adaptive immune system in order to continue the fight against an invader that has not been eradicated[1].

Adaptive response

A slower but longer-lasting and specific defence composed of lymphocytes (B and T cells). T cells both attack the invader and signal B cell production. B cells recognise the antigen and proliferate, differentiating into antibody-producing plasma cells[1].

Response resolution

Once an infection is eradicated, the immune system self-regulated to shut down the response and prevent host damage[2]. A portion of B cells will remain as memory cells to rapidly reactivate for the same antigen and some plasma cells survive for long periods as a source of antibodies[1].

Antigens are any molecule, such as a protein, that elicit an immune response and they can be present on both pathogens and healthy cells in the human body. Autoimmune diseases, such as MS, are caused by inappropriate immune responses to antigens on healthy human cells (called “self-antigens”), which are normally ignored by the immune system.[3]

In the currently accepted pathogenesis of MS[3,4], this response is targeted at the CNS. Lymphocytes cross the BBB and activate within the CNS, with B cells differentiating into autoantibody-producing plasma cells. These cells destroy the myelin sheath on neuronal axons and damage the neurons themselves through toxicity and production of cytokines.

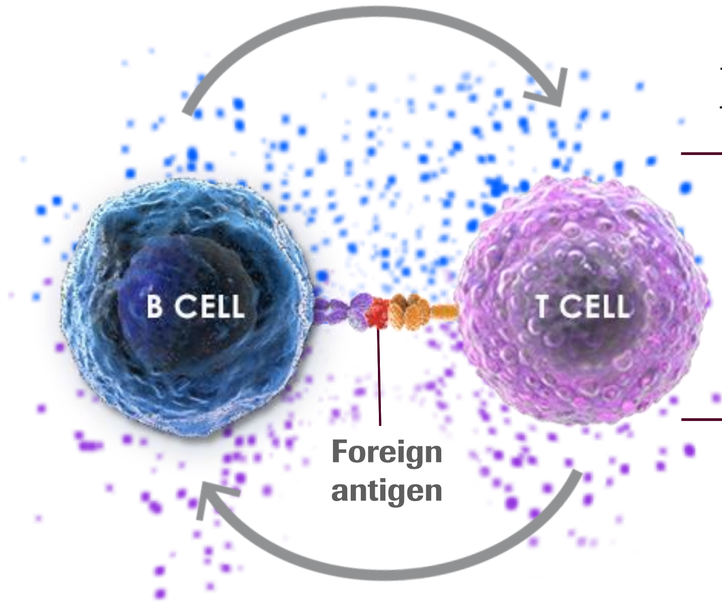
BBB, blood-brain barrier; CNS, central nervous system.

1. Murphy K (2012). Janeway’s Immunobiology. 8th Ed. Garland Science;
2. Sompayrac L (2008). How the Immune System Works. 3rd Ed. Blackwell Publishing;
3. Coyle PK (2011). MS: Pathology and Immunology. In Rizvi SA, Coyle PK (Eds.) Clinical Neuroimmunology: Multiple Sclerosis and Related Disorders (pp. 43–70). Humana Press;
4. Bar-Or A. Semin Neurol 2008;28:29–45.

B- and T-cell interactions are critical in healthy immune responses resulting in the removal of pathogens

B cells provide signals to promote T-cell responses[1,2]

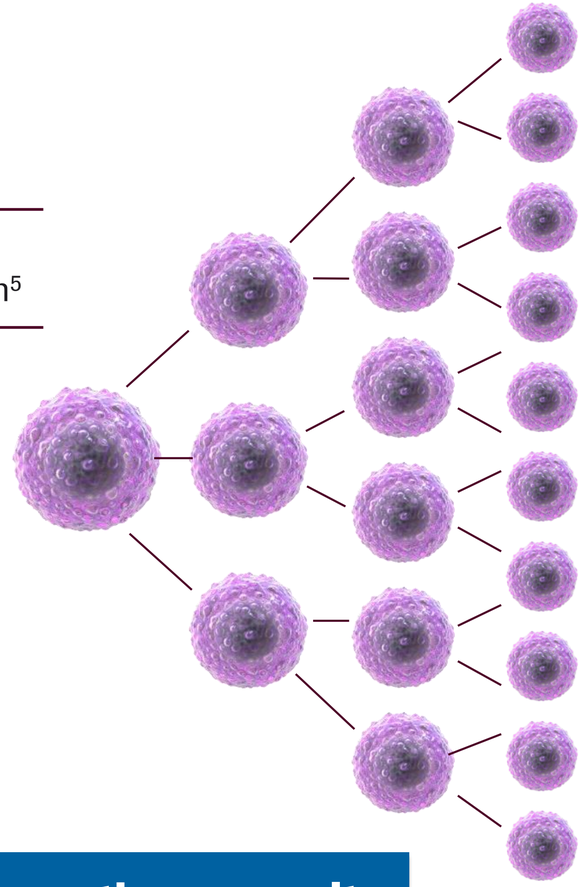
IL-6
IL-10
LTα
TGF-β
TNF-α



IL-4
IL-5
IL-10
IL-21

T cells provide “help” to B cells through the delivery of cytokines[1-4]

T-cell expansion[5]



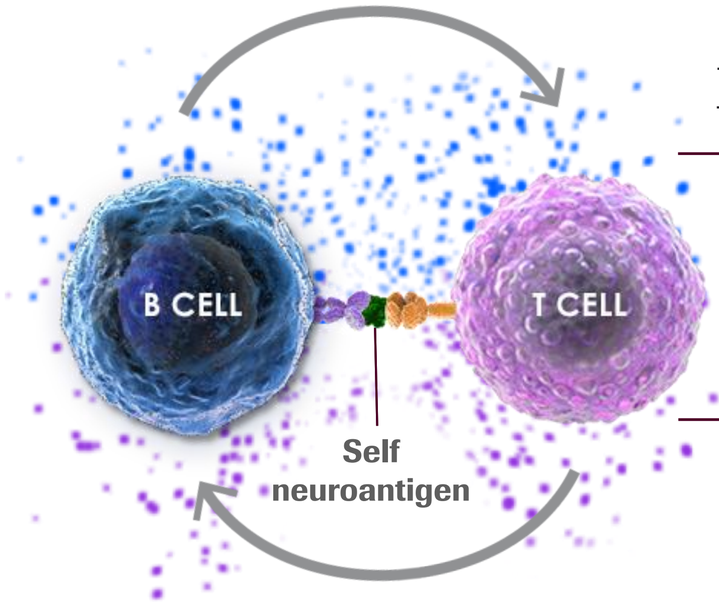
Healthy **proliferative response to a foreign antigen, results in effector-mediated killing of pathogens[6,7]**

IL, interleukin; LT, lymphotoxin; TGF, transforming growth factor; TNF, tumour necrosis factor.

1. Edwards JC, Cambridge G. Nat Rev Immunol 2006;394–403; 2. Lund FE. Curr Opin Immunol 2008;20:332–8; 3. Varzaneh FN, et al. J Clin Immunol 2014;34:524-43;
4. Kuchen S, et al. J Immunol 2007;179:5886–96; 5. Chan OT, et al. J Exp Med 1999;189:1639–47; 6. Ireland SJ, et al. Autoimmunity 2012;45:400–14; 7. Hauser SL. Mult Scler 2015;21:8–21.

B- and T-cell interactions abnormally respond to self neuroantigens in MS, resulting in autoimmunity

B cells provide signals to promote T-cell responses[1,2]

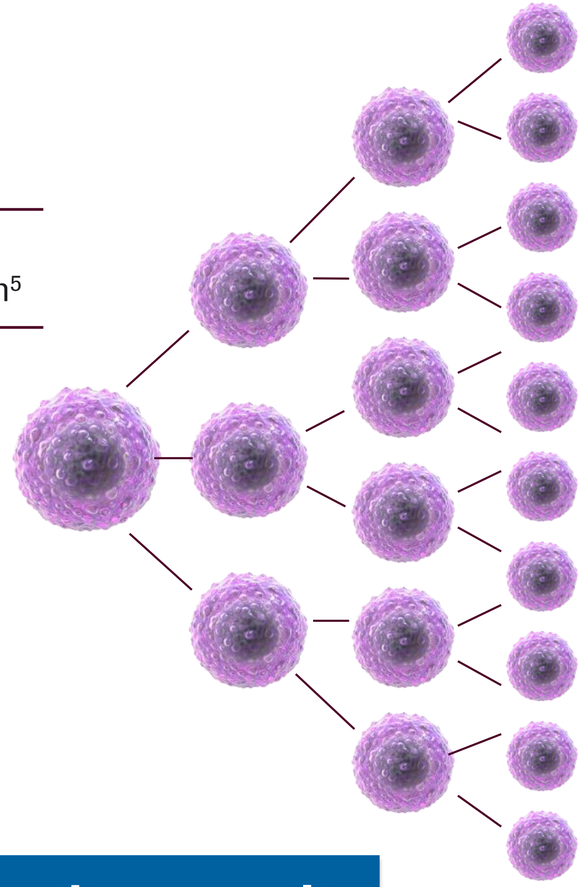


T cells provide “help” to B cells through the delivery of cytokines[1-4]

IL-6
IL-10
LTα
TGF-β
TNF-α

IL-4
IL-5
IL-10
IL-21

T-cell expansion[5]



An *auto*reactive response to self neuroantigens results in the degradation of components of the CNS[6]

IL, interleukin; LT, lymphotoxin; TGF, transforming growth factor; TNF, tumour necrosis factor.

1. Edwards JC, Cambridge G. Nat Rev Immunol 2006;394–403; 2. Lund FE. Curr Opin Immunol 2008;20:332–8; 3. Varzaneh FN, et al. J Clin Immunol 2014;34:524-43;
4. Kuchen S, et al. J Immunol 2007;179:5886–96; 5. Chan OT, et al. J Exp Med 1999;189:1639–47; 6. Ireland SJ, et al. Autoimmunity 2012;45:400–14; 7. Hauser SL. Mult Scler 2015;21:8–21.

In immune-mediated diseases, the processes normally preventing the activation of autoreactive B and T cells are dysfunctional

There are four potential hypotheses for the activation autoreactive B and T cells:

Molecular mimicry

Foreign antigens share sequence or structural homology with self-antigens leading to the production of self-reactive T cells.[1]

Novel autoantigen presentation

Citrullination of proteins expands the repertoire of epitopes after protein immunisation. Citrullination is increased during inflammation, potentially leading to novel autoantigen presentation.[2]

Recognition of sequestered antigens

Self-reactive T cells are produced in response to sequestered autoantigens released to the periphery following a viral infection.[3]

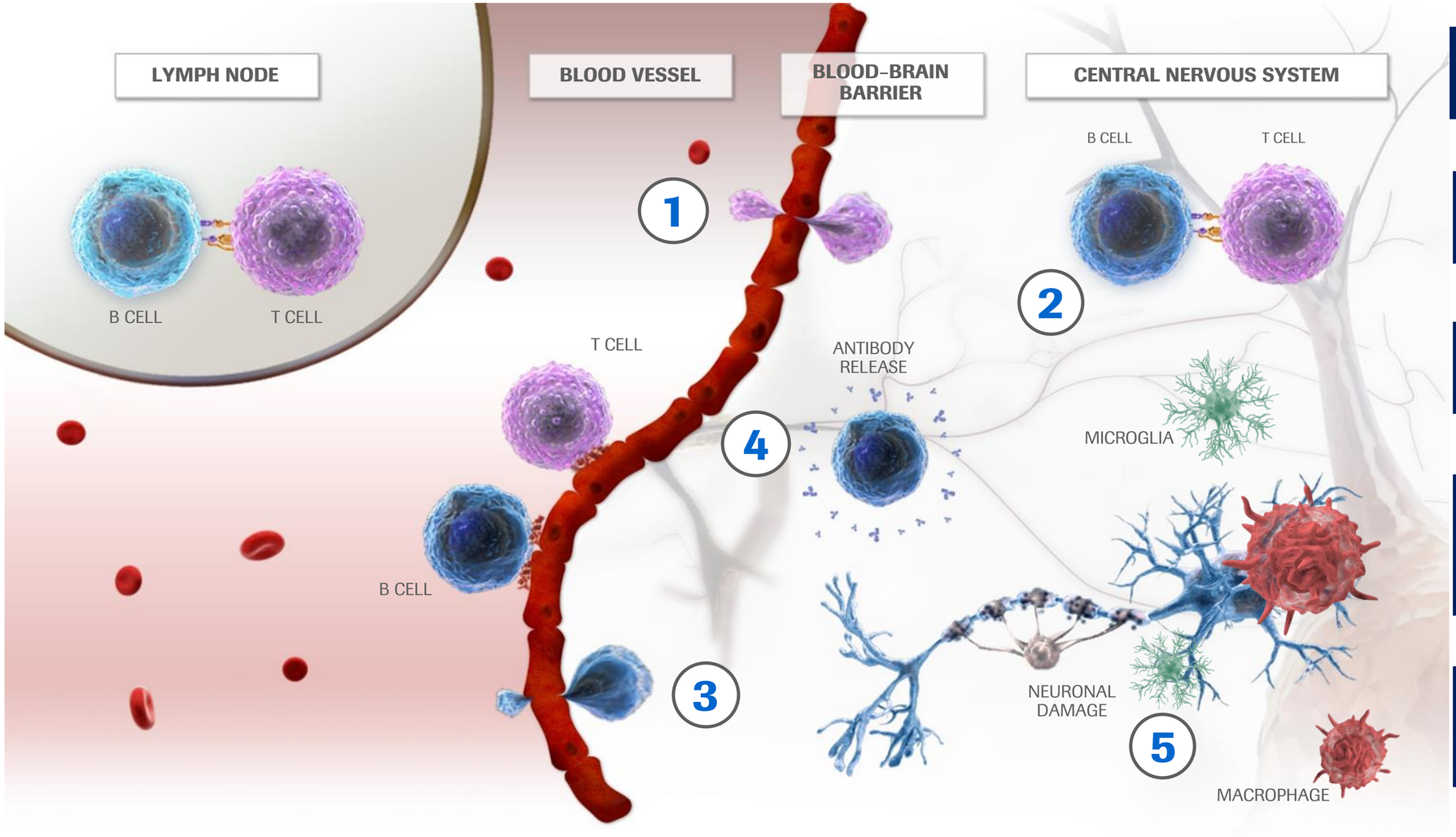
Bystander activation

Autoreactive cells are activated during infection due to nonspecific inflammatory events.[1]

Once the immune system has targeted an autoantigen to the CNS, the antigen is never removed and results in a continuous cycle of inflammation and damage

1. Sospedra M, Martin R. Annu. Rev Immunol 2005;23:683–747; 2. Faigle W, et al .Front Immunol 2019:540; 3. Miller SD, et al. Nature Med 1997;3:1133–6.

Immune cell infiltration into the CNS in early MS leads to demyelination promoted by microglia and astrocytes



1. Following activation in the periphery, autoreactive T cells and B cells adhered to the CNS move across the BBB[1,2]
2. Lymphocytes undergo another level of activation, mediated by APCs upregulated as part of the inflammatory response[1,2]
3. Autoreactive lymphocytes, primarily Th1 cells, promote the recruitment and activities of other mediators of damage[1,2]
4. B cells differentiate into plasma cells and produce autoantibodies directed against CNS tissue, which causes damage to myelin via opsonisation and activation of the complement cascade[3]
5. Cytotoxic T cells, macrophages and microglia attack and damage myelin, oligodendrocytes, and axons – via a combination of direct and indirect mechanisms[1]

APC, antigen-presenting cell; BBB, blood–brain barrier; CNS, central nervous system; Th, T helper cell.

1. Bar-Or A. Semin Neurol 2008;28:29–45; 2. Dendrou CA, et al. Nat Rev Immunol 2015;15:545–58; 3. Weber MS, et al. Biochim Biophys Acta 2011;1812:239–45.

An overview of immune cells and their specific roles in relation to the neuropathology of MS

	Innate			Adaptive		
Cell types	**Macrophages**	**Microglia**	**Astrocytes**	**B cells**	**T cells**	
					CD4	**CD8**
Hypothesised immune function in MS	· Antigen-independent inflammation · Immediate response[3] · Antigen presentation	· Cytokine production[14] · Increased ROS production · Antigen presentation	· Cytokine production[17] · Recruitment of leukocytes across the BBB · Increased ROS production	· Antigen presentation[1] · Cytokine production[2] · Antibody production (humoral immunity)[1,3] · Formation of lymphoid follicles* that potentiate selective immune cell formation[1–6] · Enhanced response by repeated antigen exposure (memory)[3]	· Helper T cell7 · Concentrated in the perivascular cuff7 · Cytokine production8 · Co-stimulation of B cells · Enhanced response by repeated antigen exposure (memory)3	· Cytotoxic T cell7 · Widely distributed within the parenchyma7 · Antigen-dependent cell-mediated cytotoxicity · Cytokine production2 · Enhanced response by repeated antigen exposure (memory)3
Cytokines released when activated	IL-1β, TNF-α, IFN-γ[12]	IL-1β, IL-6, TNF-α[15]	IL-1β, IL-6, IL-10, TNF-α[17]	IFN-γ, IL-6, IL-10[12]	· IL-10, TGF-β, IL-4, IL-17, IL-21, IL-22, IFN-γ10	· IL-17, IFN-γ, GM-CSF, TNF, TGF-β11
Cell surface markers	CD40, CD86, FcγRI (CD64), FcγRII (CD32)[13]	CD11b, F4/80, CD115, MHC-II, CD45, CD11c CD68[16]	MHC-II, CD11a, CD54, CD80, CD86[17]	CD19, CD20, CD52, α4-Intergrin, BAFF-R[9]	· NKG2C, CD56, NKG2D, granzyme B11	· MCAM, CD25, CD122, CD5611

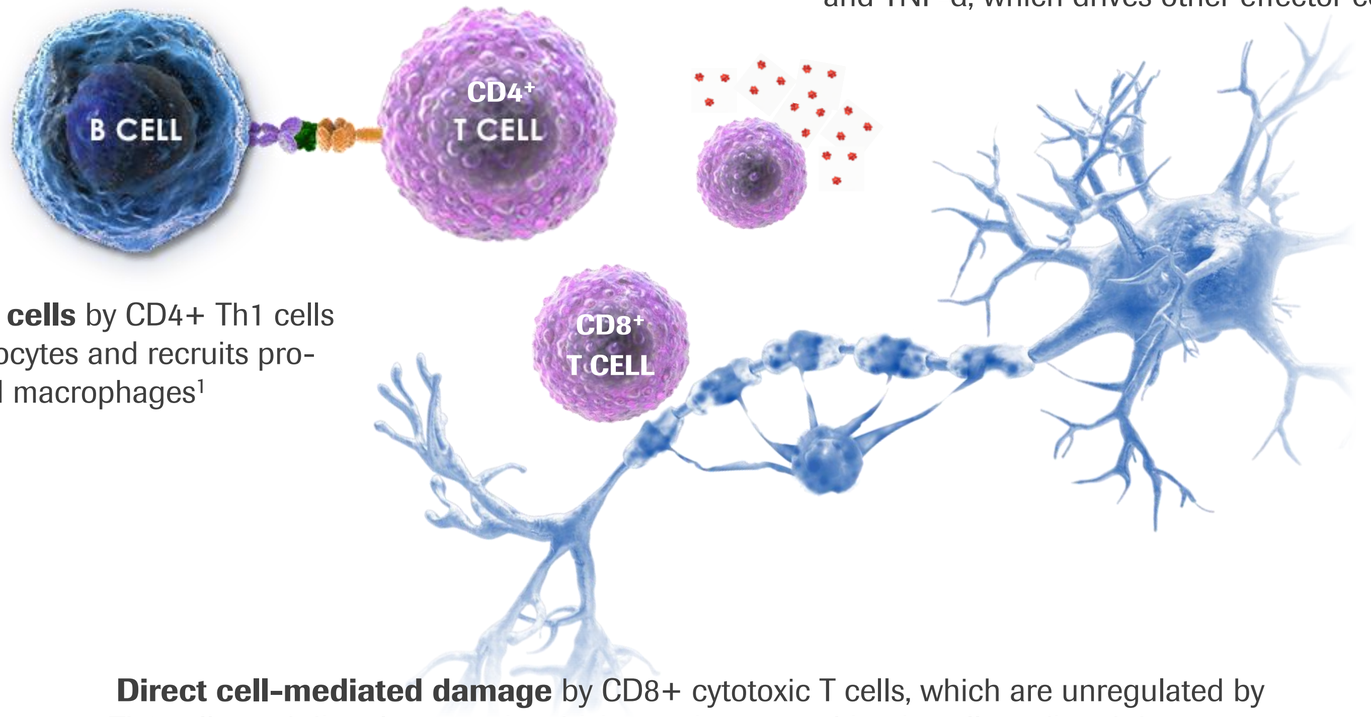
*Usually in lymphoid tissue, but ectopic lymphoid follicles can be found in the brains of patients with MS5,6

BBB, blood-brain barrier; GM-CSF, granulocyte macrophage colony stimulating factor; IFN, interferon; IL, interleukin; MCAM, melanoma cell adhesion module; MHC, major histocompatibility complex; ROS, ; TNF, tumour necrosis factor. 1. Parkin J, Cohen B. Lancet 2001;357:1777–89; 2. LeBien TW, Tedder TF. Blood 2008;112:1570–80; 3. Warrington R, et al. Allergy Asthma Clin Immunol 2011;7:S1; 4. Chaplin DD. J Allergy Clin Immunol 2010;125:S3–23; 5. Serafini B, et al. Brain Pathol 2004;14:164–74; 6. Magliozzi R, et al. Ann Neurol 2010;68:477–93; 7. Reich DS, et al. N Engl J Med 2018;378:169–80; 8. Delves P, Roitt I. N Engl J Med 2000;343:37–49; 9. Krumbholz M, et al. Nat Rev Neurol 2012;8:613–23; 10. Fletcher JM, et al. Clin Exp Immunol 2010;162:1–11; 11. Legroux L, Arbour N. J Neuroimmune Pharmacol 2015;10:528–54; 12. Rawji KS, Wee Yong V. Clin Dev Immunol 2013:948–76; 13. Vogel DYS, et al. J Neuroinflammation 2013;35; 14. Carson MJ. Glia 2002;40:218–31; 15. Hanisch U. Glia 2002;40:140–55; 16. Greter M, et al. Front Immunol 2015;6:249; 17. Ponath G, et al. Front Immunol 2018;9:217.

T cells play key roles in acute inflammation in MS via the recruitment of additional pro-inflammatory cells to the CNS

Co-stimulatory activation of B cells

Pro-inflammatory cytokine production primarily by CD4+ Th1 cells, e.g. production of IFN-γ and TNF-α, which drives other effector cells[2]



Recruitment of pro-inflammatory cells by CD4+ Th1 cells promotes CNS infiltration of lymphocytes and recruits pro-inflammatory microglia and macrophages[1]

Direct cell-mediated damage by CD8+ cytotoxic T cells, which are unregulated by Th1 cells, and directly recognise driving antigens resulting in cell-mediated damage to myelin, oligodendrocytes and axons[2]

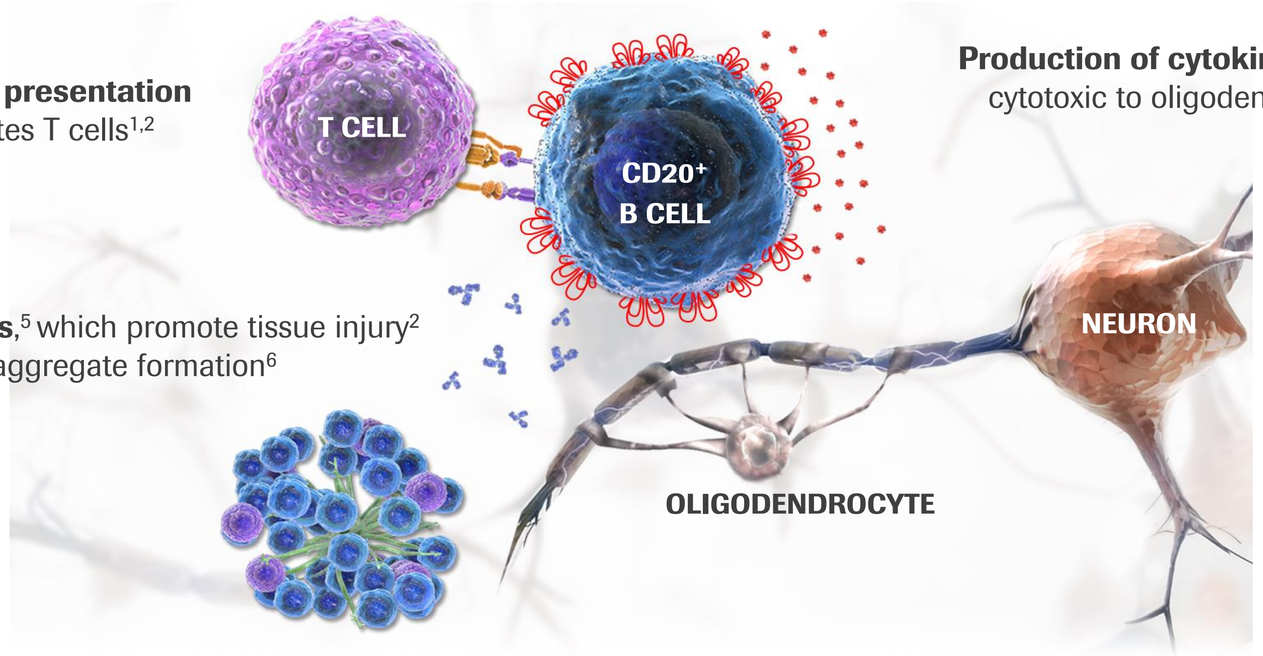
CNS, central nervous system; IFN, interferon; Th, T helper cell; TNF, tumour necrosis factor.

1. Dendrou CA, et al. Nat Rev Immunol 2015;15:545–58;
2. Filippi M, et al. Nat Rev Dis Primers 2018;4:43.

B cells activate T cells, produce cytokines and autoantibodies and are present in ectopic lymphoid follicle-like aggregates

Antigen presentation activates T cells[1,2]

Production of autoantibodies,[5] which promote tissue injury[2] and drive lymphoid aggregate formation[6]



Production of cytokines,[2,3] some of which are cytotoxic to oligodendrocytes and neurons[4]

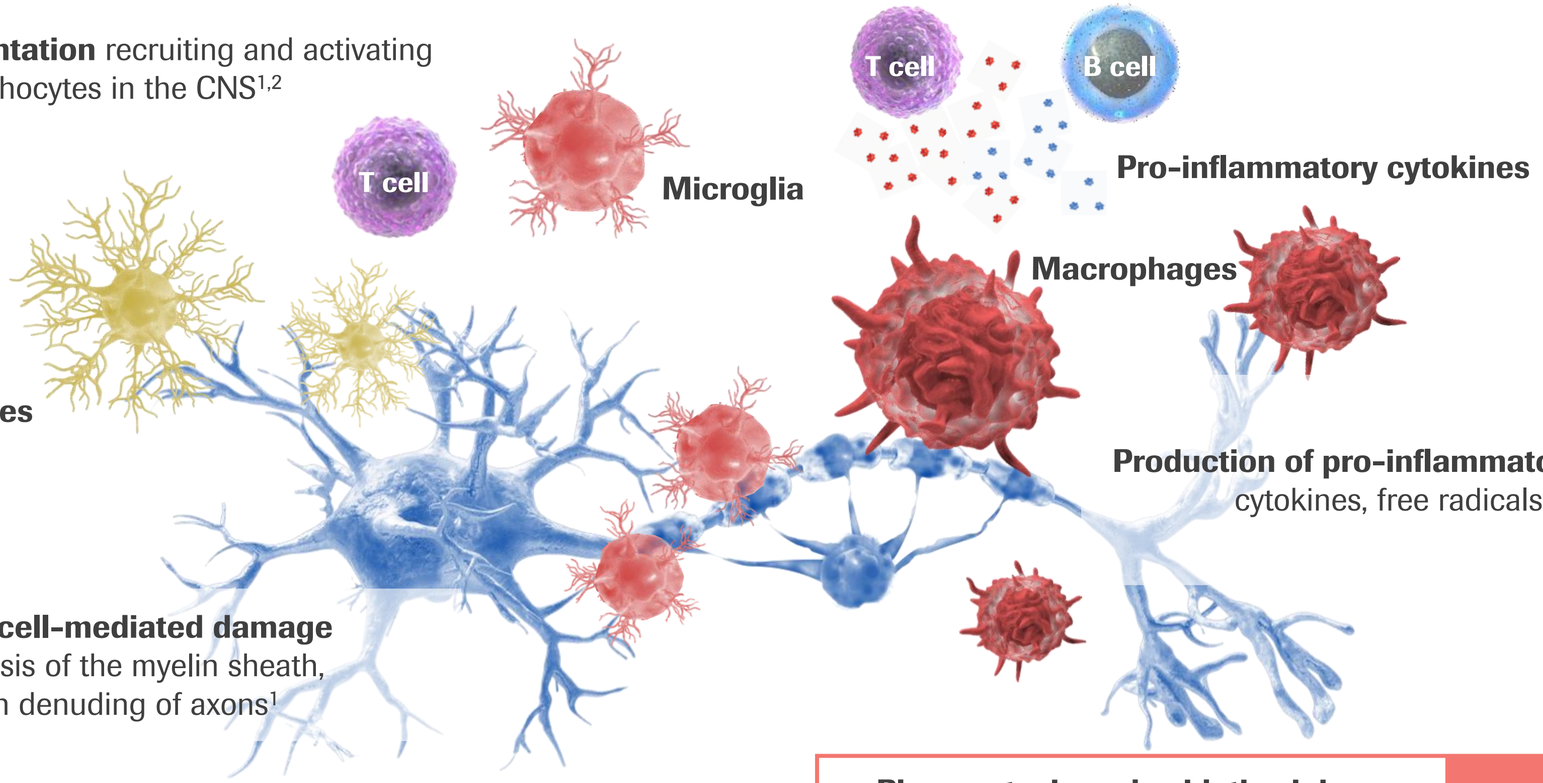
Ectopic lymphoid follicle-like aggregates maintain the autoreactive responses in close proximity to the target tissues[6,7]

Driver of chronic inflammation (mostly seen in SPMS)

SPMS, secondary progressive MS.

1. Crawford A, et al. J Immunol 2006;176:3498–506; 2. Bar-Or A, et al. Ann Neurol 2010;67:452–6; 3. Lisak RP, et al. J Neuroimmunol 2012;246:85–95;
4. Lisak RP, et al. J Neuroimmunol 2017;309:88–99; 5. Weber MS, et al. Biochim Biophys Acta 2011;1812:239–45; 6. Serafini B, et al. Brain Pathol 2004;14:164–74;
7. Magliozzi R, et al. Ann Neurol 2010;68:477–93.

Microglia and macrophages of the innate immune system also play key roles in both acute and chronic inflammation



CNS, central nervous system.

1. Dendrou CA, et al. Nat Rev Immunol 2015;15:545–58;
2. Filippi M, et al. Nat Rev Dis Primers 2018;4:43.

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Il futuro della medicina, l’avanguardia di noi medici.

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