

REVIEW ARTICLE

The role of astrocytes in multiple sclerosis pathogenesis[☆]

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PALABRAS CLAVE

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Inflamación del SNC;
Complejo principal de histocompatibilidad;
Linfocitos T;
Barrera hematoencefálica;
Citocinas

Abstract

Introduction: Multiple sclerosis (MS) is a demyelinating autoimmune disease of the central nervous system (CNS), in which astrocytes play an important role as CNS immune cells. However, the activity of astrocytes as antigen-presenting cells (APC) continues to be subject to debate. **Development:** This review analyses the existing evidence on the participation of astrocytes in CNS inflammation in MS and on several mechanisms that modify astrocyte activity in the disease.

Conclusion: Astrocytes play a crucial role in the pathogenesis of MS because they express toll-like receptors (TLR) and major histocompatibility complex (MHC) class I and II. In addition, astrocytes participate in regulating the blood-brain barrier (BBB) and in modulating T cell activity through the production of cytokines. Future studies should focus on the role of astrocytes in order to find new therapeutic targets for the treatment of MS.

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Participación de los astrocitos en la patogénesis de la esclerosis múltiple

Resumen

Introducción: La esclerosis múltiple (EM) es una enfermedad autoinmune desmielinizante del sistema nervioso central (SNC) en la que los astrocitos tienen una participación importante como células inmunes del SNC, aunque su actividad como células presentadoras de antígeno (APC) aún es discutida.

Desarrollo: En la presente revisión se analiza la evidencia existente sobre la participación de los astrocitos en la inflamación del SNC en la EM, así como diversos mecanismos que modifican su actividad en la enfermedad.

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Conclusiones: Los astrocitos desempeñan un papel trascendental en la patogénesis de la EM, debido a que expresan receptores TLR, así como proteínas del complejo principal de histocompatibilidad (MHC) clase I y II. Además, participan en la regulación de la barrera hematoencefálica (BHE) y la modulación de la actividad de los linfocitos T mediante la producción de citocinas. Futuros estudios deberán enfocarse en el papel de los astrocitos con el objetivo de encontrar nuevos blancos terapéuticos para el tratamiento de la EM.

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Introduction

Multiple sclerosis (MS) is a demyelinating autoimmune disease of the central nervous system (CNS)^{1–3} presenting great clinical heterogeneity.⁴ It has been associated with numerous genetic and environmental risk factors.⁵ The disease is characterised by the appearance of lesions or plaques⁶ formed by CNS cells and immune system cells, which migrate across the blood-brain barrier (BBB) and induce CNS inflammation.⁷ T cells and macrophages are the main mediators of CNS inflammation; these cells invade the CNS and modulate the activity of glial cells and neurons through different cell mechanisms, leading to demyelination and cell death in patients with MS.⁸

Astrocytes are the most abundant type of glial cells in the CNS⁹ and play a dual role in MS pathogenesis¹⁰: firstly, they contribute to disease progression, acting as CNS immune cells and secreting chemokines that promote immune cell migration from the peripheral blood to the CNS¹⁰; and secondly, they promote the migration, proliferation, and differentiation of oligodendrocyte precursor cells,¹¹ favouring remyelination. The available evidence suggests that the role of astrocytes should be reevaluated, as these cells not only provide support and contribute to maintaining homeostasis, but also play a major role in the pathogenesis of CNS autoimmune diseases, particularly MS.

In the light of these considerations, the purpose of this study is to review, summarise, and discuss the available evidence on the role of astrocytes in MS pathogenesis. This review addresses the following points: 1) the role of astrocytes as CNS immune cells in the MS inflammatory process; 2) the role of astrocytes as antigen-presenting cells (APC); 3) the role of astrocytes in BBB integrity and some mechanisms altering BBB permeability, which enables immune cell migration into the CNS; and 4) the role of astrocytes in T cell regulation.

Astrocytes as immune cells in multiple sclerosis

As is the case with microglia, astrocytes express pattern recognition receptors (PRR), which bind to pathogen-associated molecular patterns (PAMP).¹² PRRs recognise PAMPs derived from different pathogenic microorganisms, such as bacteria^{13,14} and viruses,^{15,16} as well as damage-associated molecular patterns (DAMP), which are considered to be host-derived and are released after cell damage or death.¹⁷ Astrocytes express toll-like receptors TLR3 and TLR4.¹² TLR3 recognises double-stranded RNA released by

damaged or virus-infected cells, inducing a proinflammatory response in the immune system¹⁸ through TRIF-, NF- κ B-, RIP1-, and TRAF6-dependent signalling.¹⁹ However, Bsibsi et al.²⁰ showed that TLR3-mediated astrocyte activation in the CNS induces overproduction of anti-inflammatory cytokines interleukin (IL)-9, IL-10, and IL-11, and decreases the expression of the p40 subunit of IL-12 and IL-13. Furthermore, TLR3 expression by astrocytes may be enhanced by interferon (IFN)- γ , IFN- β , or IL-1 β .²¹ This suggests that TLR3 expression in patients with MS modulates inflammation through the expression of anti-inflammatory cytokines, which limit the activity of immune cells.

TLR4 is upregulated in brain lesions of animals with experimental autoimmune encephalomyelitis (EAE), an experimental model of MS, as well as in blood cells from patients with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS).²² Crowley et al.²³ report that TLR4 and TLR3 activation with an inflammatory stimulus in patients with MS enhances NF- κ B expression, increasing TNF- α levels. This finding supports the hypothesis that astrocytes play a dual role in MS: on the one hand, TLR3 activation in astrocytes releases anti-inflammatory cytokines that limit neuroinflammation, and on the other hand, TLR3 and TLR4 stimulation may promote a proinflammatory process secondary to increased TNF- α production.

Astrocytes as antigen-presenting cells in multiple sclerosis

Astrocytes are non-traditional APCs,²⁴ since they only serve an immune function if CNS damage is present.²⁵ Astrocytes constitutively express major histocompatibility complex (MHC) class I molecules.²⁶ However, MHC class II expression in astrocytes is controversial: while some studies suggest that MHC class II molecules are constitutively expressed in astrocytes,²⁷ others report minimal expression²⁸ or suggest that expression is cytokine-dependent.²⁹ There is also controversy around the expression of co-stimulatory molecules: some studies suggest that astrocytes can express co-stimulatory molecules of the B7 family,^{30,31} whereas others have found no evidence of B7 molecule expression.^{32,33} In any case, it seems clear that such infectious processes as viral infections induce MHC class I and II expression in astrocytes,^{34,35} and that expression of both classes of MHC

molecules changes according to the predominant cytokine profile in the CNS.^{27,36–38}

Biopsy studies of post mortem brain tissue from patients with MS have detected MHC class I³⁹ and II^{40,41} molecules in astrocytes (Fig. 1). T cells present in MS lesions induce MHC class I overexpression through IFN- γ production,⁴² which is regulated by NF- κ B activity.²⁶ IFN- γ production also increases MHC class II expression^{27,36,43} through increased activity of protein kinase C and IFN-gamma enhanced factor X; the latter interacts with the X box of the DRA promoter.⁴⁴ Furthermore, IFN- γ increases the mobility of MHC class II compartments, which is intermediate filament- dependent, allowing faster delivery of MHC molecules to the surface of astrocytes.³⁶ This suggests that astrocytes may constitutively express MHC class II molecules, which remain in intracellular compartments until astrocytes are stimulated by IFN- γ .

However, MHC expression in astrocytes may be inhibited by different molecules. One of the first molecules to be analysed was IFN- β , which blocks IFN- γ - induced MHC class II expression^{45,46} without modifying MHC class I expression.⁴⁶ This immunomodulatory effect is used as an action mechanism in IFN- β treatment for MS,^{47–49} which was approved by the United States Food and Drug Administration in 1993.⁵⁰ It delays relapses, decreases neurological deterioration, and slows disease progression.⁵⁰

Other cytokines associated with modulation of MHC class II expression in astrocytes are IL-4,³⁸ IL-1,²⁷ and TGF- β .⁵¹ TGF- β , the most extensively studied cytokine, is known to decrease MHC class II expression in astrocytes^{51,52} and other types of cells.^{53,54} Dong et al.⁵⁵ showed that TGF- β inhibits the expression of the MHC class II transactivator (CIITA), which is needed for the induction of EAE,⁵⁶ and the activity of the CIITA type IV promoter through the Smad3 transcription factor.⁵⁵

Some studies suggest that MHC expression is regulated by molecules directly involved in nerve transmission. Similarly, it is reported that glutamate,⁵⁷ norepinephrine,^{57,58} and gangliosides^{59,60} may inhibit MHC expression in astrocytes. Furthermore, serotonin may modify the response of immune system cells.^{61,62} Serotonin receptor agonists are known to inhibit the expression of IFN- γ -induced MHC class II molecules and B7 co-stimulatory molecules in astrocytes.⁶³ Seddighzadeh et al.⁶⁴ found an interaction between a protective haplotype in serotonin receptor HTR2A alleles and HLA-DRB1 alleles constitutively expressed in synovial fibroblasts from patients with rheumatoid arthritis, a widely studied autoimmune disease. Since astrocytes regulate synapse formation,⁶⁵ changes in neurotransmitter release may alter MHC expression in astrocytes and their involvement in T cell antigen presentation.

Furthermore, oestrogen has been found to have a neuroprotective effect, as it induces an anti-inflammatory response in astrocytes, decreasing the severity of EAE and MS^{66,67} through different mechanisms. One of these is the modulation of astrocytes' activity as APCs. Adamski et al.⁶⁸ showed that oestrogen decreases MHC class II expression in astrocytes through a mechanism independent of CIITA expression, attenuating histone acetylation in the MHC class II promoter (Fig. 2). Oestrogen has also been

found to decrease the expression of cluster of differentiation (CD) 40 and CD86 in microglia⁶⁹; in professional APCs (dendritic cells, macrophages, and B cells), it increases expression of programmed cell death protein 1.⁷⁰ This suggests that oestrogen may also modulate the expression of co-stimulatory molecules in astrocytes (Fig. 2).

Astrocytes modulate blood-brain barrier permeability in multiple sclerosis

Astrocytes present close contact with the basal lamina of the BBB, since their processes line blood vessel walls.⁷¹ At this level, astrocytes are interconnected by gap junctions formed by connexin 43 and connexin 30.¹⁰ Brand-Schieber et al.⁷² observed decreased expression of connexin 43 in astrocytes from mice with EAE, which suggests loss of connectivity between astrocytes and increased BBB permeability. Furthermore, astrocytes express aquaporin-4,⁷¹ which has been shown to be overexpressed in active MS lesions⁷³ (Fig. 1). In a more recent study of rats with post-traumatic brain injury conducted by Soltani et al.,⁷⁴ oestrogen was found to decrease aquaporin-4 expression (Fig. 2), which may suggest a protective effect on the BBB in EAE and MS.

Furthermore, astrocytes can modulate BBB permeability through cytokine production. The combination of cytokines produced by astrocytes depends on their interactions with other cells and the stimuli received from other cytokines. Production of IL-1 β , IL-6, and TNF- α by astrocytes increases BBB permeability, whereas production of TGF- β has the opposite effect.⁷⁵ Furthermore, the BBB transports cytokines bidirectionally (blood to brain, brain to blood),⁷⁶ which means that systemic overproduction of proinflammatory cytokines promotes inflammation associated with the underlying CNS disease.

Immune cells in the peripheral blood have limited access to the CNS. To enter the CNS, cells must migrate via diapedesis through the BBB to the perivascular space, and then to the brain parenchyma²⁵; astrocytes are the first CNS cells to be activated by T cells, due to their direct contact with the BBB.⁷⁷ IL-17 production by Th17 cells and subsequent Act1-mediated IL-17 signalling induce the production of chemokines that increase immune cell recruitment and diapedesis through the BBB.^{77,78} Thus, interaction between Th17 cells and astrocytes may trigger inflammation in MS due to astrocyte activation and production of soluble factors (chemokines and cytokines), which increase BBB permeability.

The role of astrocytes in the expression of the Th1/Th2/Th17 profile

Th1 and Th17 cells are the CD4+ T cell lineages responsible for inflammation in MS, whereas Th2 and Treg cells limit inflammatory activity.⁷⁹ Several studies have addressed the role of astrocytes on the modulation of the Th1/Th2/Th17 profile in the CNS. Astrocytes have been found to pro-

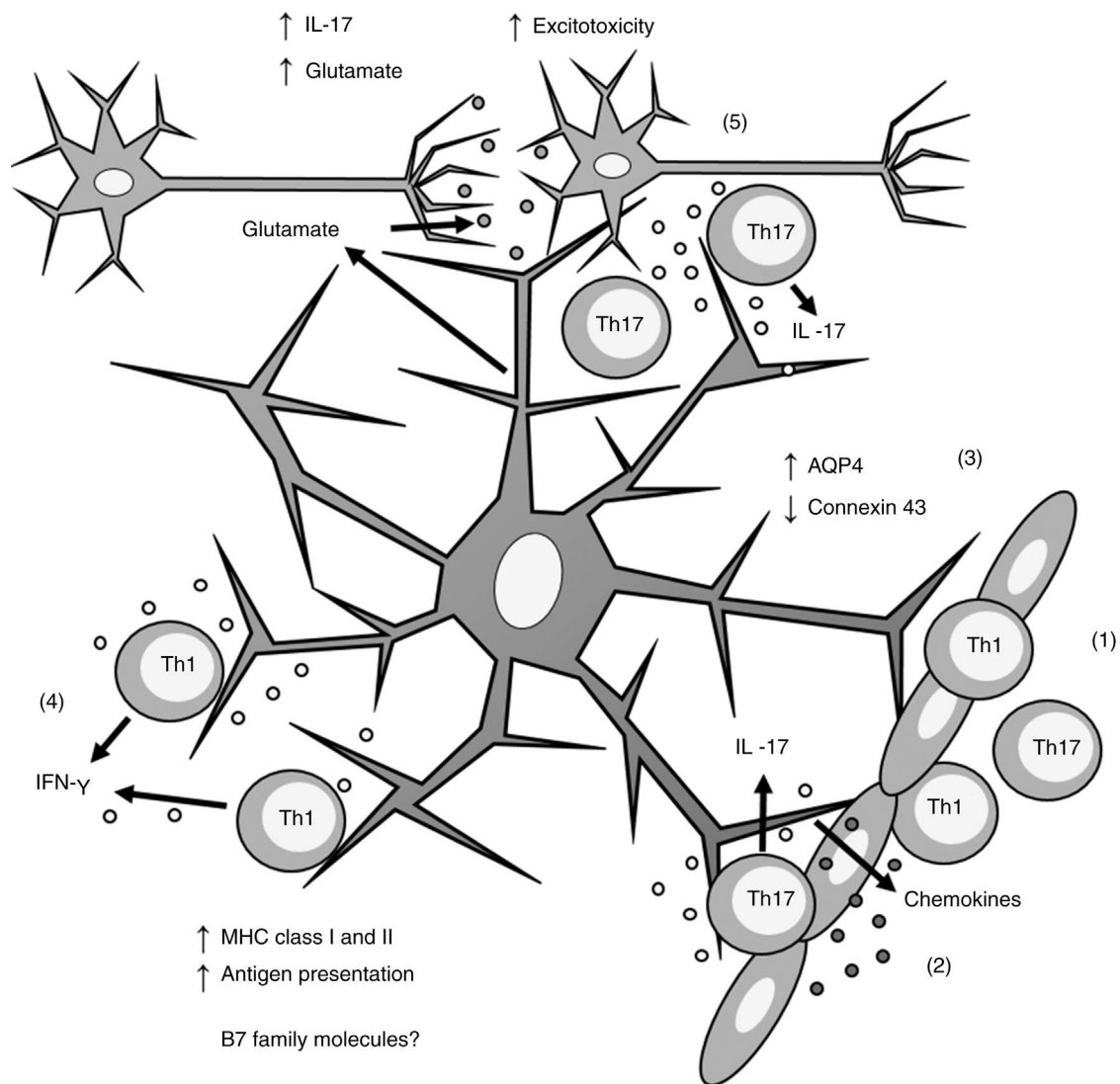


Figure 1 Role of astrocytes on the pathogenesis of multiple sclerosis. 1) Th1 and Th17 cells cross the blood-brain barrier through diapedesis; 2) Th17 cells produce IL-17, which induces chemokine production by astrocytes, increasing immune cell recruitment; 3) astrocytes overexpress AQP4 and decrease the expression of connexin 43; 4) Th1 cells produce IFN- γ , which induces MHC class I and II overexpression in astrocytes; this in turn increases antigen presentation; 5) Th17 cells produce IL-17, which induces an increase in glutamate levels in the synaptic region, leading to excitotoxicity and neuronal death.

AQP4: aquaporin-4; IFN- γ : interferon γ ; IL-17: interleukin 17; MHC: major histocompatibility complex; Th1: T helper 1 cell; Th17: T helper 17 cell.

duce cytokines from the IL-12 family, such as IL-12,^{80,81} IL-23 (both p40^{80,81} and p19 subunits⁸¹), and IL-27 (both p28 and EBI3 subunits).⁸² In MS, production of these cytokines seems to determine the predominant profile over the course of the disease; this is addressed later in the review.

On the one hand, IL-12 and IL-23 production favours the presence of Th1 and Th17 cells, respectively.⁸³ As both cytokines share the p40 subunit, previous studies have shown that IL-23 is essential in MS pathogenesis, since presence of IL-23-induced Th17⁸⁴ in the absence of Th1 is sufficient to induce EAE in animals.^{85,86} Therefore, there is a correlation between presence of IL-23

and severity of disease induced by IL-17,⁸⁴ which induced excitotoxicity and neuronal death due to glutamate accumulation in the synaptic region^{65,87} (Fig. 1). On the other hand, when IL-12 production is promoted, Th1 cells are the predominant population⁸³; therefore, IFN- γ production inhibits differentiation into Th17 lineage cells.⁸⁸ This suggests that IL-23 production by astrocytes promotes CNS inflammation through Th17-dependent mechanisms, and that IL-12 production partially promotes inflammation via Th1. However, increased IL-12 production suggests that the predominant population is Th1, which together with subsequent IFN- γ production regulates the activity of the Th17 population.

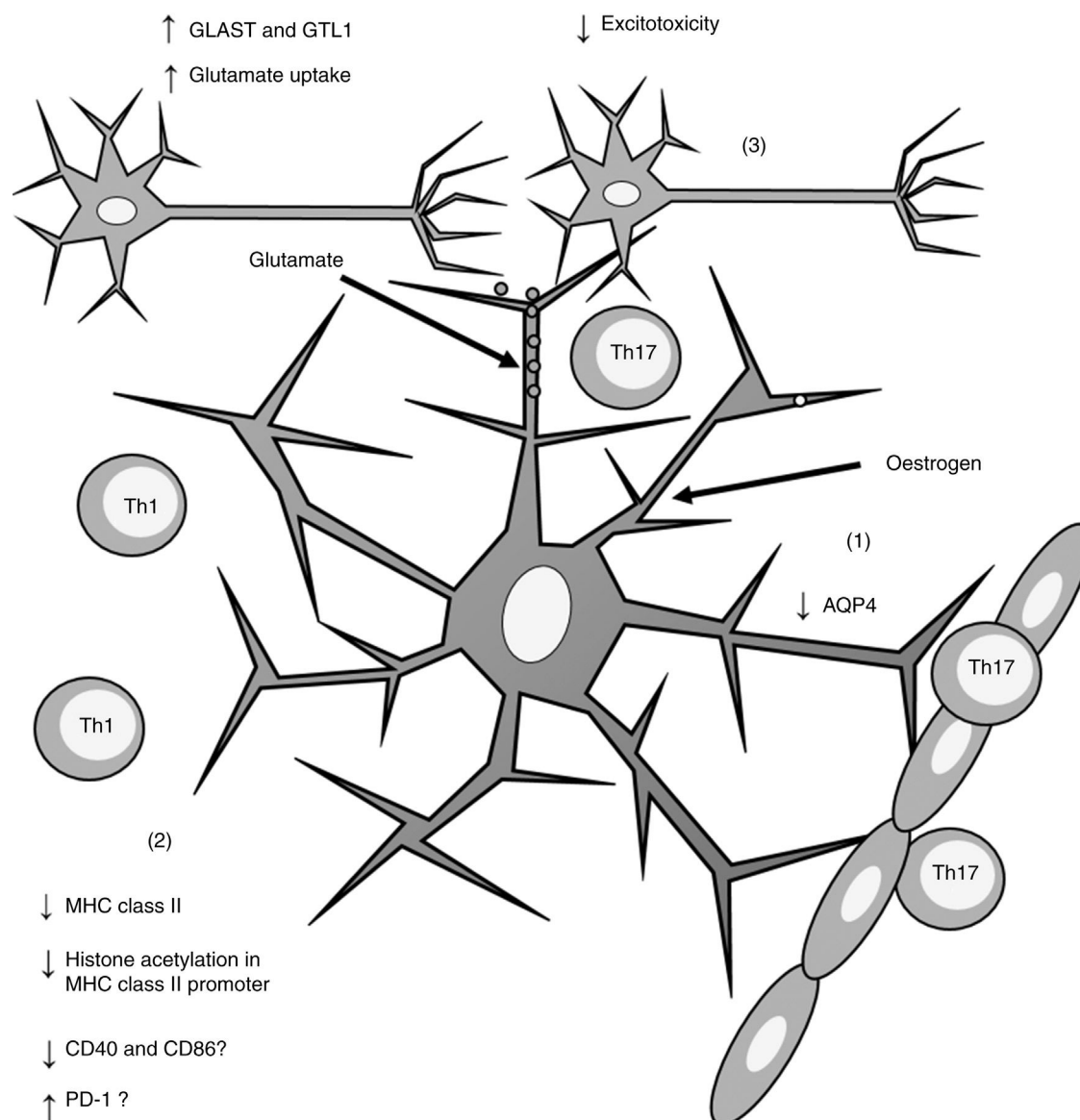


Figure 2 Effects of oestrogen on astrocytes. Oestrogen decreases AQP4 expression (1); decreases MHC class II expression, which in turn reduces antigen presentation (2); and increases the expression of GLAST and GTL1, which increases glutamate uptake in neuronal synapses and reduces excitotoxicity (3).

AQP4: aquaporin-4; CD40: cluster of differentiation 40; CD86: cluster of differentiation 86; GLAST: glutamate aspartate transporter; GTL1: glutamate transporter-1; MHC: major histocompatibility complex; PD-1: programmed cell death protein 1; Th1: T helper 1 cell; Th17: T helper 17 cell.

Regarding IL-17-mediated glutamate excitotoxicity, several studies have shown that oestrogen increases the expression of the glutamate aspartate transporter^{66,89–91} and glutamate transporter-1 in astrocytes.^{66,90–92} This suggests that oestrogen plays a neuroprotective role in astrocytes by increasing glutamate reuptake in the synaptic region,^{66,90} which may decrease neuronal death secondary to excessive glutamate activity (Fig. 2).

IL-27 is extensively produced by astrocytes and microglia in patients with MS, and its receptor is expressed by both T cells and astrocytes.⁸² IL-27 mainly has anti-inflammatory

effects and has been found to limit the development of EAE in animals as it regulates Th1 and Th2 cell response through a decrease in IL-2 levels, which limits the proliferation of these populations.⁸³ Furthermore, IL-27 decreases Th17 cell differentiation^{93,94} and, together with IL-6, may induce IL-10 production in Th1, Th2, and Th17 cells.⁹⁵ This suggests that astrocytes modulate the inflammatory response in MS through various mechanisms, including IL-27 secretion by astrocytes and microglia, inducing a self-limiting process due to IL-10 production by different T cell populations.

Conclusions

Astrocytes play a major role in MS pathogenesis since they are actively involved in CNS inflammation and also limit inflammation through several mechanisms, including: 1) expression of TLRs, which enable astrocytes to act as immune cells; 2) expression of MHC class I and II molecules, as well as co-stimulatory molecules, which allows astrocytes to serve as professional APCs; 3) regulation of BBB permeability; and 4) production of IL-12, IL-23, and IL-27, which regulate the expression of Th1 and Th17 inflammatory profiles in the CNS. Furthermore, there is evidence suggesting that oestrogen has a neuroprotective effect on the mechanisms involving astrocytes. Future studies should address the role of astrocytes and modulation of their activity in CNS inflammatory processes with a view to finding new therapeutic targets for MS.

Conflicts of interest

The author has no conflicts of interest to declare.

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References

- Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med*. 2000;343:938–52.
- Bruck W. The pathology of multiple sclerosis is the result of focal inflammatory demyelination with axonal damage. *J Neurol*. 2005;252 Suppl 5:v3–9.
- Lassmann H. Multiple sclerosis: lessons from molecular neuropathology. *Exp Neurol*. 2014;262 Pt A:2–7.
- Disanto G, Berlanga AJ, Handel AE, Para AE, Burrell AM, Fries A, et al. Heterogeneity in multiple sclerosis: scratching the surface of a complex disease. *Autoimmune Dis*. 2010;2011:932351.
- Guerrero-Garcia JJ, Carrera-Quintanar L, Lopez-Roa RI, Marquez-Aguirre AL, Rojas-Mayorquin AE, Ortuno-Sahagun D. Multiple sclerosis and obesity: possible roles of adipokines. *Mediators Inflamm*. 2016;2016:4036232.
- Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol*. 2000;47:707–17.
- Sospedra M, Martin R. Immunology of multiple sclerosis. *Annu Rev Immunol*. 2005;23:683–747.
- Steinman L. Immunology of relapse and remission in multiple sclerosis. *Annu Rev Immunol*. 2014;32:257–81.
- He F, Sun YE. Glial cells more than support cells? *Int J Biochem Cell Biol*. 2007;39:661–5.
- Correale J, Farez MF. The role of astrocytes in multiple sclerosis progression. *Front Neurol*. 2015;6:180.
- Moore CS, Abdullah SL, Brown A, Arulpragasam A, Crocker SJ. How factors secreted from astrocytes impact myelin repair. *J Neurosci Res*. 2011;89:13–21.
- Farina C, Aloisi F, Meinl E. Astrocytes are active players in cerebral innate immunity. *Trends Immunol*. 2007;28:138–45.
- Echchannaoui H, Frei K, Schnell C, Leib SL, Zimmerli W, Landmann R. Toll-like receptor 2-deficient mice are highly susceptible to *Streptococcus pneumoniae* meningitis because of reduced bacterial clearing and enhanced inflammation. *J Infect Dis*. 2002;186:798–806.
- Shen Y, Kawamura I, Nomura T, Tsuchiya K, Hara H, Dewamitta SR, et al. Toll-like receptor 2- and MyD88-dependent phosphatidylinositol 3-kinase and Rac1 activation facilitates the phagocytosis of *Listeria monocytogenes* by murine macrophages. *Infect Immun*. 2010;78:2857–67.
- Kurt-Jones EA, Chan M, Zhou S, Wang J, Reed G, Bronson R, et al. Herpes simplex virus 1 interaction with Toll-like receptor 2 contributes to lethal encephalitis. *Proc Natl Acad Sci U S A*. 2004;101:1315–20.
- Poteet E, Lewis P, Chen C, Ho SO, Do T, Chiang S, et al. Toll-like receptor 3 adjuvant in combination with virus-like particles elicit a humoral response against HIV. *Vaccine*. 2016;34:5886–94.
- Prinz M, Garbe F, Schmidt H, Mildner A, Gutcher I, Wolter K, et al. Innate immunity mediated by TLR9 modulates pathogenicity in an animal model of multiple sclerosis. *J Clin Invest*. 2006;116:456–64.
- Chattopadhyay S, Sen GC. dsRNA-activation of TLR3 and RLR signaling: gene induction-dependent and independent effects. *J Interferon Cytokine Res*. 2014;34:427–36.
- Kawai T, Akira S. Antiviral signaling through pattern recognition receptors. *J Biochem*. 2007;141:137–45.
- Bsibi M, Persoon-Deen C, Verwer RW, Meeuwse S, Ravid R, Van Noort JM. Toll-like receptor 3 on adult human astrocytes triggers production of neuroprotective mediators. *Glia*. 2006;53:688–95.
- Farina C, Krumbholz M, Giese T, Hartmann G, Aloisi F, Meinl E. Preferential expression and function of Toll-like receptor 3 in human astrocytes. *J Neuroimmunol*. 2005;159:12–9.
- Andersson A, Covacu R, Sunnemark D, Danilov AI, Dal Bianco A, Khademi M, et al. Pivotal advance: HMGB1 expression in active lesions of human and experimental multiple sclerosis. *J Leukoc Biol*. 2008;84:1248–55.
- Crowley T, Fitzpatrick JM, Kuijper T, Cryan JF, O'Toole O, O'Leary OF, et al. Modulation of TLR3/TLR4 inflammatory signaling by the GABAB receptor agonist baclofen in glia and immune cells: relevance to therapeutic effects in multiple sclerosis. *Front Cell Neurosci*. 2015;9:284.
- Chastain EM, Duncan DS, Rodgers JM, Miller SD. The role of antigen presenting cells in multiple sclerosis. *Biochim Biophys Acta*. 2011;1812:265–74.
- Sofroniew MV. Astrocyte barriers to neurotoxic inflammation. *Nat Rev Neurosci*. 2015;16:249–63.
- Massa PT, Ozato K, McFarlin DE. Cell type-specific regulation of major histocompatibility complex (MHC) class I gene expression in astrocytes, oligodendrocytes, and neurons. *Glia*. 1993;8:201–7.
- Gresser O, Hein A, Riese S, Regnier-Vigouroux A. Tumor necrosis factor alpha and interleukin-1 alpha inhibit through different pathways interferon-gamma-induced antigen presentation,

- processing and MHC class II surface expression on astrocytes, but not on microglia. *Cell Tissue Res.* 2000;300:373–82.
28. Hamo L, Stohlman SA, Otto-Duessel M, Bergmann CC. Distinct regulation of MHC molecule expression on astrocytes and microglia during viral encephalomyelitis. *Glia.* 2007;55:1169–77.
 29. Vidovic M, Sparacio SM, Elovitz M, Benveniste EN. Induction and regulation of class II major histocompatibility complex mRNA expression in astrocytes by interferon-gamma and tumor necrosis factor-alpha. *J Neuroimmunol.* 1990;30:189–200.
 30. Zeinstra E, Wilczak N, De Keyser J. Reactive astrocytes in chronic active lesions of multiple sclerosis express co-stimulatory molecules B7-1 and B7-2. *J Neuroimmunol.* 2003;135:166–71.
 31. Soos JM, Ashley TA, Morrow J, Patarroyo JC, Szenté BE, Zamvil SS. Differential expression of B7 co-stimulatory molecules by astrocytes correlates with T cell activation and cytokine production. *Int Immunol.* 1999;11:1169–79.
 32. Cross AH, Ku G. Astrocytes and central nervous system endothelial cells do not express B7-1 (CD80) or B7-2 (CD86) immunoreactivity during experimental autoimmune encephalomyelitis. *J Neuroimmunol.* 2000;110:76–82.
 33. Satoh J, Lee YB, Kim SU. T-cell costimulatory molecules B7-1 (CD80) and B7-2 (CD86) are expressed in human microglia but not in astrocytes in culture. *Brain Res.* 1995;704:92–6.
 34. Liu Y, King N, Kesson A, Blanden RV, Mullbacher A. Flavivirus infection up-regulates the expression of class I and class II major histocompatibility antigens on and enhances T cell recognition of astrocytes in vitro. *J Neuroimmunol.* 1989;21:157–68.
 35. Hirayama M, Miyadai T, Yokochi T, Sato K, Kubota T, Iida M, et al. Infection of human T-lymphotropic virus type I to astrocytes in vitro with induction of the class II major histocompatibility complex. *Neurosci Lett.* 1988;92:34–9.
 36. Vardjan N, Gabrijel M, Potokar M, Svajger U, Kreft M, Jeras M, et al. IFN-gamma-induced increase in the mobility of MHC class II compartments in astrocytes depends on intermediate filaments. *J Neuroinflamm.* 2012;9:144.
 37. Jarosinski KW, Massa PT. Interferon regulatory factor-1 is required for interferon-gamma-induced MHC class I genes in astrocytes. *J Neuroimmunol.* 2002;122:74–84.
 38. Morga E, Heuschling P. Interleukin-4 down-regulates MHC class II antigens on cultured rat astrocytes. *Glia.* 1996;17:175–9.
 39. Ransohoff RM, Estes ML. Astrocyte expression of major histocompatibility complex gene products in multiple sclerosis brain tissue obtained by stereotactic biopsy. *Arch Neurol.* 1991;48:1244–6.
 40. Frank E, Pulver M, de Tribolet N. Expression of class II major histocompatibility antigens on reactive astrocytes and endothelial cells within the gliosis surrounding metastases and abscesses. *J Neuroimmunol.* 1986;12:29–36.
 41. Zeinstra E, Wilczak N, Streefland C, De Keyser J. Astrocytes in chronic active multiple sclerosis plaques express MHC class II molecules. *Neuroreport.* 2000;11:89–91.
 42. Hirayama M, Yokochi T, Shimokata K, Iida M, Fujiki N. Induction of human leukocyte antigen-A,B,C and -DR on cultured human oligodendrocytes and astrocytes by human gamma-interferon. *Neurosci Lett.* 1986;72:369–74.
 43. Pulver M, Carrel S, Mach JP, de Tribolet N. Cultured human fetal astrocytes can be induced by interferon-gamma to express HLA-DR. *J Neuroimmunol.* 1987;14:123–33.
 44. Panek RB, Lee YJ, Itoh-Lindstrom Y, Ting JP, Benveniste EN. Characterization of astrocyte nuclear proteins involved in IFN-gamma- and TNF-alpha-mediated class II MHC gene expression. *J Immunol.* 1994;153:4555–64.
 45. Barna BP, Chou SM, Jacobs B, Yen-Lieberman B, Ransohoff RM. Interferon-beta impairs induction of HLA-DR antigen expression in cultured adult human astrocytes. *J Neuroimmunol.* 1989;23:45–53.
 46. Satoh J, Paty DW, Kim SU. Differential effects of beta and gamma interferons on expression of major histocompatibility complex antigens and intercellular adhesion molecule-1 in cultured fetal human astrocytes. *Neurology.* 1995;45:367–73.
 47. Kurtuncu M, Tuzun E, Turkoglu R, Petek-Balci B, Icoz S, Pehlivan M, et al. Effect of short-term interferon-beta treatment on cytokines in multiple sclerosis: significant modulation of IL-17 and IL-23. *Cytokine.* 2012;59:400–2.
 48. Dressel A, Kolb AK, Elitok E, Bitsch A, Bogumil T, Kitz B, et al. Interferon-beta1b treatment modulates cytokines in patients with primary progressive multiple sclerosis. *Acta Neurol Scand.* 2006;114:368–73.
 49. Khademi M, Wallstrom E, Andersson M, Piehl F, Di Marco R, Olsson T. Reduction of both pro- and anti-inflammatory cytokines after 6 months of interferon beta-1a treatment of multiple sclerosis. *J Neuroimmunol.* 2000;103:202–10.
 50. Loma I, Heyman R. Multiple sclerosis: pathogenesis and treatment. *Curr Neuroparmacol.* 2011;9:409–16.
 51. Schluesener HJ. Transforming growth factors type beta 1 and beta 2 suppress rat astrocyte autoantigen presentation and antagonize hyperinduction of class II major histocompatibility complex antigen expression by interferon-gamma and tumor necrosis factor-alpha. *J Neuroimmunol.* 1990;27:41–7.
 52. Lee YJ, Han Y, Lu HT, Nguyen V, Qin H, Howe PH, et al. TGF-beta suppresses IFN-gamma induction of class II MHC gene expression by inhibiting class II transactivator messenger RNA expression. *J Immunol.* 1997;158:2065–75.
 53. Czarnecki CW, Chiu HH, Wong GH, McCabe SM, Palladino MA. Transforming growth factor-beta 1 modulates the expression of class II histocompatibility antigens on human cells. *J Immunol.* 1988;140:4217–23.
 54. Reimold AM, Kara CJ, Rooney JW, Glimcher LH. Transforming growth factor beta 1 repression of the HLA-DR alpha gene is mediated by conserved proximal promoter elements. *J Immunol.* 1993;151:4173–82.
 55. Dong Y, Tang L, Letterio JJ, Benveniste EN. The Smad3 protein is involved in TGF-beta inhibition of class II transactivator and class II MHC expression. *J Immunol.* 2001;167:311–9.
 56. Stuve O, Youssef S, Slavin AJ, King CL, Patarroyo JC, Hirschberg DL, et al. The role of the MHC class II transactivator in class II expression and antigen presentation by astrocytes and in susceptibility to central nervous system autoimmune disease. *J Immunol.* 2002;169:6720–32.
 57. Lee SC, Collins M, Vanguri P, Shin ML. Glutamate differentially inhibits the expression of class II MHC antigens on astrocytes and microglia. *J Immunol.* 1992;148:3391–7.
 58. Frohman EM, Vayuvegula B, van den Noort S, Gupta S. Norepinephrine inhibits gamma-interferon-induced MHC class II (Ia) antigen expression on cultured brain astrocytes. *J Neuroimmunol.* 1988;17:89–101.
 59. Massa PT. Specific suppression of major histocompatibility complex class I and class II genes in astrocytes by brain-enriched gangliosides. *J Exp Med.* 1993;178:1357–63.
 60. Massa PT, Wu C. Modulation of major histocompatibility complex class I genes by interferon-gamma and ganglioside GT 1b in astrocytes: involvement of protein tyrosine phosphatases. *J Neurochem.* 1996;67:1831–9.

61. Abdouh M, Storrington JM, Riad M, Paquette Y, Albert PR, Drobetsky E, et al. Transcriptional mechanisms for induction of 5-HT1A receptor mRNA and protein in activated B and T lymphocytes. *J Biol Chem*. 2001;276:4382–8.
62. Sternberg EM, Trial J, Parker CW. Effect of serotonin on murine macrophages: suppression of Ia expression by serotonin and its reversal by 5-HT2 serotonergic receptor antagonists. *J Immunol*. 1986;137:276–82.
63. Zeinstra EM, Wilczak N, Wilschut JC, Glazenburg L, Chesik D, Kroese FG, et al. 5HT4 agonists inhibit interferon-gamma-induced MHC class II and B7 costimulatory molecules expression on cultured astrocytes. *J Neuroimmunol*. 2006;179:191–5.
64. Seddighzadeh M, Korotkova M, Kallberg H, Ding B, Dahan N, Kurreeman FA, et al. Evidence for interaction between 5-hydroxytryptamine (serotonin) receptor 2A and MHC type II molecules in the development of rheumatoid arthritis. *Eur J Hum Genet*. 2010;18:821–6.
65. Kostic M, Zivkovic N, Cvetanovic A, Stojanovic I, Colic M. IL-17 signalling in astrocytes promotes glutamate excitotoxicity: Indications for the link between inflammatory and neurodegenerative events in multiple sclerosis. *Mult Scler Relat Disord*. 2017;11:12–7.
66. Karki P, Smith K, Johnson J Jr, Lee E. Astrocyte-derived growth factors and estrogen neuroprotection: role of transforming growth factor- α in estrogen-induced upregulation of glutamate transporters in astrocytes. *Mol Cell Endocrinol*. 2014;389:58–64.
67. Chakrabarti M, Haque A, Banik NL, Nagarkatti P, Nagarkatti M, Ray SK. Estrogen receptor agonists for attenuation of neuroinflammation and neurodegeneration. *Brain Res Bull*. 2014;109:22–31.
68. Adamski J, Ma Z, Nozell S, Benveniste EN. 17 β -Estradiol inhibits class II major histocompatibility complex (MHC) expression: influence on histone modifications and cbp recruitment to the class II MHC promoter. *Mol Endocrinol*. 2004;18:1963–74.
69. Dimayuga FO, Reed JL, Carnero GA, Wang C, Dimayuga ER, Dimayuga VM, et al. Estrogen and brain inflammation: effects on microglial expression of MHC, costimulatory molecules and cytokines. *J Neuroimmunol*. 2005;161:123–36.
70. Polanczyk MJ, Hopke C, Vandenbark AA, Offner H. Estrogen-mediated immunomodulation involves reduced activation of effector T cells, potentiation of Treg cells, and enhanced expression of the PD-1 costimulatory pathway. *J Neurosci Res*. 2006;84:370–8.
71. Abbott NJ, Ronnback L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci*. 2006;7:41–53.
72. Brand-Schieber E, Werner P, Iacobas DA, Iacobas S, Beelitz M, Lowery SL, et al. Connexin43, the major gap junction protein of astrocytes, is down-regulated in inflamed white matter in an animal model of multiple sclerosis. *J Neurosci Res*. 2005;80:798–808.
73. Sinclair C, Kirk J, Herron B, Fitzgerald U, McQuaid S. Absence of aquaporin-4 expression in lesions of neuromyelitis optica but increased expression in multiple sclerosis lesions and normal-appearing white matter. *Acta Neuropathol*. 2007;113:187–94.
74. Soltani Z, Khaksari M, Shahrokhi N, Mohammadi G, Mofid B, Vaziri A, et al. Effect of estrogen and/or progesterone administration on traumatic brain injury-caused brain edema: the changes of aquaporin-4 and interleukin-6. *J Physiol Biochem*. 2016;72:33–44.
75. Nair A, Frederick TJ, Miller SD. Astrocytes in multiple sclerosis: a product of their environment. *Cell Mol Life Sci*. 2008;65:2702–20.
76. Banks WA. Blood-brain barrier transport of cytokines: a mechanism for neuropathology. *Curr Pharm Des*. 2005;11:973–84.
77. Kang Z, Wang C, Zepp J, Wu L, Sun K, Zhao J, et al. Act1 mediates IL-17-induced EAE pathogenesis selectively in NG2+ glial cells. *Nat Neurosci*. 2013;16:1401–8.
78. Kebir H, Kreymborg K, Ifergan I, Dodelet-Devillers A, Cayrol R, Bernard M, et al. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat Med*. 2007;13:1173–5.
79. Damsker JM, Hansen AM, Caspi RR. Th1 and Th17 cells: adversaries and collaborators. *Ann N Y Acad Sci*. 2010;1183:211–21.
80. Constantinescu CS, Frei K, Wysocka M, Trinchieri G, Malipiero U, Rostami A, et al. Astrocytes and microglia produce interleukin-12 p40. *Ann N Y Acad Sci*. 1996;795:328–33.
81. Constantinescu CS, Tani M, Ransohoff RM, Wysocka M, Hilliard B, Fujioka T, et al. Astrocytes as antigen-presenting cells: expression of IL-12/IL-23. *J Neurochem*. 2005;95:331–40.
82. Senecal V, DeBlois G, Beauseigle D, Schneider R, Brandenburg J, Newcombe J, et al. Production of IL-27 in multiple sclerosis lesions by astrocytes and myeloid cells: Modulation of local immune responses. *Glia*. 2016;64:553–69.
83. Hunter CA. New IL-12-family members: IL-23 and IL-27, cytokines with divergent functions. *Nat Rev Immunol*. 2005;5:521–31.
84. Aggarwal S, Ghilardi N, Xie MH, de Sauvage FJ, Gurney AL. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. *J Biol Chem*. 2003;278:1910–4.
85. Becher B, Durell BG, Noelle RJ. Experimental autoimmune encephalitis and inflammation in the absence of interleukin-12. *J Clin Invest*. 2002;110:493–7.
86. Gran B, Zhang GX, Yu S, Li J, Chen XH, Ventura ES, et al. IL-12p35-deficient mice are susceptible to experimental autoimmune encephalomyelitis: evidence for redundancy in the IL-12 system in the induction of central nervous system autoimmune demyelination. *J Immunol*. 2002;169:7104–10.
87. Kostic M, Dzopalic T, Zivanovic S, Zivkovic N, Cvetanovic A, Stojanovic I, et al. IL-17 and glutamate excitotoxicity in the pathogenesis of multiple sclerosis. *Scand J Immunol*. 2014;79:181–6.
88. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol*. 2005;6:1123–32.
89. Lee ES, Sidoryk M, Jiang H, Yin Z, Aschner M. Estrogen and tamoxifen reverse manganese-induced glutamate transporter impairment in astrocytes. *J Neurochem*. 2009;110:530–44.
90. Pawlak J, Brito V, Kuppers E, Beyer C. Regulation of glutamate transporter GLAST and GLT-1 expression in astrocytes by estrogen. *Brain Res Mol Brain Res*. 2005;138:1–7.
91. Liang Z, Valla J, Sefidvash-Hockley S, Rogers J, Li R. Effects of estrogen treatment on glutamate uptake in cultured human astrocytes derived from cortex of Alzheimer's disease patients. *J Neurochem*. 2002;80:807–14.
92. Lee E, Sidoryk M, Wegrzynowicz M, Yin Z, Webb A, Son DS, Aschner M. Transforming growth factor- α mediates estrogen-induced upregulation of glutamate transporter GLT-1 in rat primary astrocytes. *Glia*. 2012;60:1024–36.
93. Batten M, Li J, Yi S, Kljavin NM, Danilenko DM, Lucas S, et al. Interleukin 27 limits autoimmune encephalomyelitis by sup-

- pressing the development of interleukin 17-producing T cells. *Nat Immunol.* 2006;7:929–36.
94. Stumhofer JS, Laurence A, Wilson EH, Huang E, Tato CM, Johnson LM, et al. Interleukin 27 negatively regulates the development of interleukin 17-producing T helper cells during chronic inflammation of the central nervous system. *Nat Immunol.* 2006;7:937–45.
95. Stumhofer JS, Silver JS, Laurence A, Porrett PM, Harris TH, Turka LA, et al. Interleukins 27 and 6 induce STAT3-mediated T cell production of interleukin 10. *Nat Immunol.* 2007;8:1363–71.