Progress in Neurobiology 127–128 (2015) 1–22

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

# The role of immune cells, glia and neurons in white and gray matter pathology in multiple sclerosis

Giulia Mallucci [a,b,1], Luca Peruzzotti-Jametti [a,1], Joshua D. Bernstock [a,c], Stefano Pluchino [a,*]

[a] Department of Clinical Neurosciences, John van Geest Centre for Brain Repair, Wellcome Trust-MRC Stem Cell Institute and NIHR Biomedical Research Centre, University of Cambridge, CB2 0PY, UK
[b] Department of Brain and Behavioural Sciences, National Neurological Institute C. Mondino, University of Pavia, 27100 Pavia, Italy
[c] National Institute of Neurological Disorders and Stroke, National Institutes of Health (NINDS/NIH), Bldg10/Rm5B06, MSC 1401, 10 Center Drive, Bethesda, MD 20892, USA

ARTICLE INFO

*Article history:*
Received 7 August 2014
Received in revised form 24 November 2014
Accepted 27 February 2015
Available online 21 March 2015

*Keywords:*
Neuroimmunology
Multiple sclerosis
Inflammation
Demyelination
Regeneration
Immune modulation

ABSTRACT

Multiple sclerosis is one of the most common causes of chronic neurological disability beginning in early to middle adult life. Multiple sclerosis is idiopathic in nature, yet increasing correlative evidence supports a strong association between one's genetic predisposition, the environment and the immune system.

Symptoms of multiple sclerosis have primarily been shown to result from a disruption in the integrity of myelinated tracts within the white matter of the central nervous system. However, recent research has also highlighted the hitherto underappreciated involvement of gray matter in multiple sclerosis disease pathophysiology, which may be especially relevant when considering the accumulation of irreversible damage and progressive disability.

This review aims at providing a comprehensive overview of the interplay between inflammation, glial/neuronal damage and regeneration throughout the course of multiple sclerosis via the analysis of both white and gray matter lesional pathology. Further, we describe the common pathological mechanisms underlying both relapsing and progressive forms of multiple sclerosis, and analyze how current (as well as future) treatments may interact and/or interfere with its pathology.

Understanding the putative mechanisms that drive disease pathogenesis will be key in helping to develop effective therapeutic strategies to prevent, mitigate, and treat the diverse morbidities associated with multiple sclerosis.



**Contents**

1. Introduction . . . 2
   1.1. Pathogenesis of multiple sclerosis . . . 3
2. Inflammation . . . 4
   2.1. White matter lesions . . . 4
      2.1.1. Relapsing remitting MS . . . 4
      2.1.2. Pre-active lesions . . . 6
      2.1.3. Progressive MS . . . 6

*Abbreviations:* APC, antigen presenting cell; BBB, blood–brain barrier; CCR, CC chemokine receptor; CIS, clinical isolated syndrome; CNPase, 2′,3′-cyclic-nucleotide 3′-phosphodiesterase; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CSF, cerebrospinal fluid; DMDs, disease-modifying drugs; EBV, Epstein-Barr virus; FDC, follicular dendritic cell; FOXP3, factor forkhead box P3; GM, grey matter; HLA, human leukocyte antigen; HSC, hematopoietic stem cell; ICAM, intercellular adhesion molecule; IFN, interferon; Ig, immunoglobulin; IL, interleukin; iNSC, induced neural stem cell; iPSC, induced pluripotent stem cell; LFA, leukocyte function-associated antigen; MAG, myelin-associated glycoprotein; MHC, major histocompatibility complex; MOG, myelin oligodendrocyte glycoprotein; MMP, matrix metalloproteinases; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSC, mesenchymal stem cell; NSC, neural stem cell; OPC, oligodendrocytes precursor cell; PET, positron emission tomography; PML, progressive multifocal leukoencephalopathy; PP, primary progressive; RR, relapsing-remitting; RXR γ, retinoid X receptor γ; SP, secondary progressive; TGF, transforming growth factor; Th, T helper cell; TNF, tumor necrosis factor; Treg, T regulatory cell; VCAM, vascular cell adhesion molecule; VLA, very late antigen; WM, white matter.

* Corresponding author. Tel.: +44 1223331163; fax: +44 1223331174.
*E-mail address:* spp24@cam.ac.uk (S. Pluchino).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.pneurobio.2015.02.003
0301-0082/

2.2. Gray matter lesions . . . 6
2.2.1. Relapsing remitting MS . . . 7
2.2.2. Progressive MS . . . 7
2.3. Meningeal infiltrates . . . 8
3. Glial and neuronal damage . . . 9
3.1. Demyelination . . . 9
3.2. Neurodegeneration . . . 10
4. Mechanisms of tissue repair and regeneration . . . 10
4.1. Remyelination . . . 10
4.2. Cortical regeneration . . . 11
5. Therapies . . . 12
5.1. Approved immune-modulatory treatments . . . 12
5.1.1. Glucocorticoids . . . 12
5.1.2. Disease-modifying drugs . . . 12
5.1.3. Autologous hematopoietic stem cell transplantation . . . 14
5.2. Novel perspectives . . . 15
5.2.1. Immune-modulatory therapies for progressive MS . . . 15
5.2.2. Regenerative and neurotrophic molecules . . . 15
5.2.3. Cellular therapies . . . 15
6. Conclusions . . . 16
Acknowledgements . . . 16
References . . . 16

## 1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the human central nervous system (CNS) (Compston and Coles, 2002, 2008). Recently, the International Advisory Committee on clinical trials in MS refined the two different MS phenotypes (i.e. relapsing and progressive) on the basis of both (i) disease activity and (ii) disease progression (Lublin et al., 2014) (Table 1).

Clinical isolated syndrome (CIS), which was not included in the initial clinical descriptors (Lublin and Reingold, 1996), is now recognized as the inceptive clinical presentation of a disease that displays the characteristics of an inflammatory demyelinating disorder that has yet to fulfill the criteria necessary to diagnose MS (Miller et al., 2005a,b). CIS may be either active or inactive [as defined by the clinical assessment of relapse occurrence and/or magnetic resonance imaging (MRI) activity] (Lublin et al., 2014) and typically involves the optic nerve, brainstem/cerebellum, spinal cord, or cerebral hemispheres (Polman et al., 2011). If CIS is active and fulfills current MS diagnostic criteria, the syndrome transitions to relapsing-remitting (RR) MS (Polman et al., 2011).

RR MS may also be active or inactive, and is characterized by discrete episodes of acute neurological deficits and/or worsening of a given neurological function (i.e. relapse), followed by a complete or partial recovery (i.e. remission) (Lublin and Reingold, 1996). RR MS is the most common phenotype of MS (accounting for ~85% of total cases), it displays a clear association with sex (female to male prevalence is between 2:1 and 3:1), and develops in young adults between the ages of 20 and 30 years (Confavreux et al., 1980).

Progressive MS includes secondary progressive (SP) and primary progressive (PP) MS, both of which can be either active or inactive (as per the above) and the disease course may develop with or without progression (measured by clinical evaluation which is assessed at a minimum annually) (Lublin et al., 2014). Recent data estimate that within 5 and 15 years of an initial diagnosis of MS, 25 and 75% of patients respectively, will go on to develop SP MS (Scalfari et al., 2014). Thus the probability of disease progression increases in accordance with time after initial disease onset (Scalfari et al., 2014). Unfortunately, to date there are no clinical, imaging, immunological or pathological criteria that

**Table 1**
Major characteristics of MS forms as classified by (Lublin et al., 2014).

| Clinical form | Disease course |
|---|---|
| Clinical isolated syndrome (CIS) | Characterized by acute or sub acute onset of monophasic episode suggestive of MS, that has yet to fulfill the current MS criteria. The episode lasts more than 24 h and usually affects the optic nerve, brain stem or spinal cord<br>Between 30% and 70% of patients with a CIS develop MS:<br>In patients with optic neuritis CIS conversion to MS varies between 10% and 85%<br>In patients with brainstem syndromes CIS conversion to MS varies between 50% and 60%<br>In patients with spinal cord CIS conversion to MS varies between 40% and 60%<br>Age of onset between 20 and 45 years<br>Female to male ratio between 2:1 and 5:1 |
| Relapsing-remitting MS (RR MS) | Characterized by relapses over days to weeks, followed by complete or partial remissions over months or years<br>~85% of cases<br>Age of onset between 20 and 30 years<br>Female to male ratio between 2:1 and 3:1 |
| Progressive MS<br>Secondary Progressive MS (SP MS)<br>Primary Progressive MS (PP MS) | Characterized by progressive accumulation of disability after initial relapsing course of the disease<br>~75% of RR MS cases within 15 years of the initial diagnosis<br>Characterized by steady functional worsening from the onset of the disease<br>~15% of cases<br>Later onset than RR MS (~10 years)<br>Female to male ratio: 1:1 |