Autoimmunity Reviews 13 (2014) 1070–1078

Contents lists available at ScienceDirect

Autoimmunity Reviews

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

Review

Peripheral nerve proteins as potential autoantigens in acute and chronic inflammatory demyelinating polyneuropathies

Jia Pei Lim [a], Jérôme Devaux [b], Nobuhiro Yuki [a,c,*]

[a] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Unit 09-01, Centre for Translational Medicine, 14 Medical Drive, 117599, Singapore
[b] Aix-Marseille Université, CNRS, CRN2M-UMR7286, 13344 Marseille cedex 15, Marseille, France
[c] Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Unit 09-01, Centre for Translational Medicine, 14 Medical Drive, 117599, Singapore

ARTICLE INFO

Article history:
Received 12 June 2014
Accepted 27 June 2014
Available online 27 August 2014

Keywords:
Autoantibody
Acute inflammatory demyelinating polyneuropathy
Charcot–Marie–Tooth disease
Chronic inflammatory demyelinating polyneuropathy
Experimental autoimmune neuritis
Guillain–Barré syndrome

ABSTRACT

Guillain–Barré syndrome is classified into acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy. Whereas autoantibodies to GM1 or GD1a induce the development of acute motor axonal neuropathy, pathogenic autoantibodies have yet to be identified in acute inflammatory demyelinating polyneuropathy and chronic inflammatory demyelinating polyneuropathy. This review highlights the importance of autoantibodies to peripheral nerve proteins in the physiopathology of acute and chronic inflammatory demyelinating polyneuropathies. Moreover, we listed up other potential antigens, which may become helpful biomarkers for acquired, dysimmune demyelinating neuropathies based on their critical functions during myelination and their implications in hereditary demyelinating neuropathies.

Contents

1. Introduction

Guillain–Barré syndrome (GBS), characterized by the acute flaccid paralysis, consists of 2 major subtypes, acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) [1,2]. Chronic inflammatory demyelinating polyneuropathy (CIDP) is characterized by progressive limb weakness over 8 weeks and is regarded as the chronic counterpart of GBS [3]. AIDP was originally presumed to be a T-cell–mediated disease [4]. However, complement deposits along the outer surface of Schwann cells without any T-cells at the peripheral nerves in some AIDP patients, suggesting that autoantibodies to myelin antigens activate complement and cause demyelination [5]. Plasma exchange is effective for GBS and CIDP, indicating that humoral factors such as autoantibodies participate in both conditions [2,3].

In AMAN, Miller Fisher syndrome and acute ataxic neuropathy, it is currently established that gangliosides are the target antigens of autoantibodies [2,6]. Gangliosides are expressed on the axonal membrane and in the myelin in the peripheral nervous system (PNS) [7]. IgG

* Corresponding author at: Departments of Medicine and Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Unit 09-01, Centre for Translational Medicine, 14 Medical Drive, 117599, Singapore. Tel.: +65 65161092; fax: +65 67766872.
E-mail address: mdcyuki@nus.edu.sg (N. Yuki).

http://dx.doi.org/10.1016/j.autrev.2014.08.005
1568-9972/

anti-GM1 and anti-GD1a antibodies are strongly associated with AMAN [8,9]. IgG and complement deposits are observed at the nodal axolemma in the spinal anterior roots in patients with AMAN [5], as well as in animal model of AMAN [10]. Passive transfer of the IgG anti-GM1 or anti-GD1a antibodies along with complement produces a replica of AMAN [11,12]: these studies have established that the IgG anti-GM1 and anti-GD1a antibodies are pathogenic autoantibodies in AMAN.

In AIDP and CIDP, the implication of anti-gangliosides antibodies is not as well established. Monospecific IgG anti-GD1b antibodies were found in patients with AIDP in a study by Miyazaki *et al.* [13], but this was not confirmed by other studies [14,15]. In a report, 2 patients with AIDP or CIDP had elevated titers of IgG anti-GD3 antibodies [16], but such antibodies are more commonly associated with Miller Fisher syndrome [17]. IgG anti-LM1 antibodies were also found in AIDP patients [13]. However, AMAN patients have a higher prevalence of IgG anti-LM1 antibodies than AIDP, and larger studies are needed to determine the association of monospecific IgG anti-LM1 antibodies in AIDP [18].

Altogether, these results suggest that autoantibodies directed against axonal gangliosides do not have a direct implication in the pathogenesis of AIDP and CIDP; rather, the hallmarks of demyelination in these neuropathies suggest that autoantibodies are directed against proteins expressed on Schwann cells. Here, we critically review the pathological implication of various autoantibodies reported in AIDP or CIDP, and suggest new putative antigens based on the understanding of the function of these molecules in myelination and in hereditary demyelinating neuropathies. We will focus this review on molecules presenting extracellular domains, as these are more likely to be relevant targets of autoantibodies [19]. For instance, IgG against moesin, a cytosolic component of the microvilli surrounding the nodes, has been detected in patients with cytomegalovirus-related AIDP during the acute phase of the illness [20]. However, our attempt to reproduce these results using enzyme-linked immunosorbent assay failed to demonstrate the presence of autoantibodies against the ezrin, radixin and moesin (Miyaji and Yuki, unpublished data). This emphasizes that future studies on antibodies against intracellular molecules should be warranted [19]. Given the large heterogeneity of AIDP and CIDP, the determination of the immune targets in these diseases is a high priority goal, which may help define more efficacious treatments [21].

2. Implication of immunity toward myelin proteins

2.1. Immunity to myelin components implicated in experimental autoimmune neuritis (EAN)

The study of the autoimmune mechanisms involved in EAN, an animal model of GBS, has first motivated the search for autoantigens in peripheral nerve. EAN was first produced in rabbits by immunization against whole peripheral nerve homogenates [22]. Compact myelin

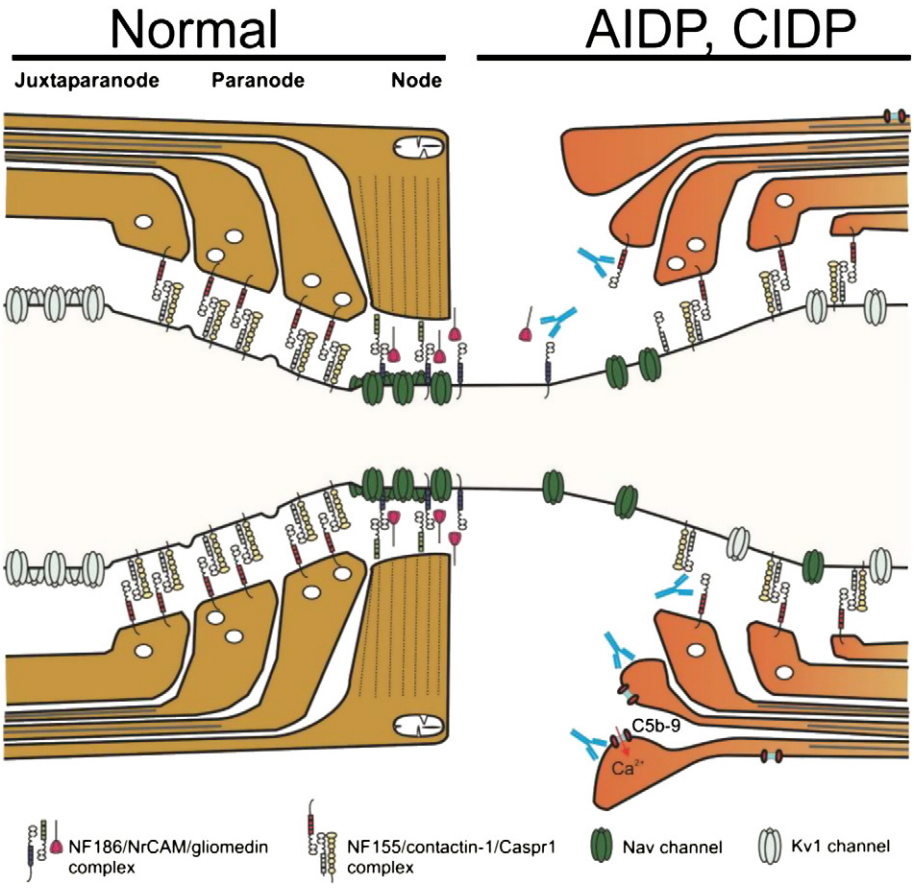

Fig. 1. Schematic illustration of the mechanisms leading to antibody-mediated demyelination in acute and chronic inflammatory demyelinating polyneuropathies. In normal myelinated fibers (left), the neurofascin 186/neuron glia-related cell adhesion molecule/gliomedin complex enables the aggregation of voltage-gated sodium channels at the nodes of Ranvier. In addition, the association of neurofascin 155/contactin-1/contactin-associated protein 1 at paranodes forms a diffusion fence that restricts the localization of voltage-gated sodium channels at the nodes and of voltage-gated potassium channels 1.1/2 at the juxtaparanodes. In acute and chronic inflammatory demyelinating polyneuropathies (right), we suspect that antibodies against cell adhesion molecules or glial proteins disrupt the axoglial interaction at the nodes and paranodes, thus leading to paranodal demyelination and to the disruption of voltage-gated sodium channel aggregates. Antibody deposition onto the glial surface may favor complement activation and the insertion of the terminal complement complex C5b-9 which might promote demyelination in acute inflammatory demyelinating polyneuropathy. AIDP, acute inflammatory demyelinating polyneuropathy; Caspr1, contactin-associated protein 1; CIDP, chronic inflammatory demyelinating polyneuropathy; Kv, voltage-gated potassium channel; Nav, voltage-gated sodium channel; NF155, neurofascin 155; NF186, neurofascin 186; and NrCAM, neuron glia-related cell adhesion molecule.