Expression of Early Growth Response Gene-2 and Regulated Cytokines Correlates with Recovery from Guillain–Barré Syndrome

Ernesto Doncel-Pérez,*[,1] Lourdes Mateos-Hernández,[†,1] Eduardo Pareja,[‡] Ángel García-Forcada,* Margarita Villar,[†] Raquel Tobes,[‡] Francisco Romero Ganuza,* Virginia Vila del Sol,* Ricardo Ramos,[§] Isabel G. Fernández de Mera,[†] and José de la Fuente[†,¶]

Guillain–Barré syndrome (GBS) is an immune-mediated peripheral neuropathy. The goal of this research was the identification of biomarkers associated with recovery from GBS. In this study, we compared the transcriptome of PBMCs from a GBS patient and her healthy twin to discover possible correlates of disease progression and recovery. The study was then extended using GBS and spinal cord injury unrelated patients with similar medications and healthy individuals. The early growth response gene-2 (EGR2) was upregulated in GBS patients during disease recovery. The results provided evidence for the implication of EGR2 in GBS and suggested a role for EGR2 in the regulation of IL-17, IL-22, IL-28A, and TNF-β cytokines in GBS patients. These results identified biomarkers associated with GBS recovery and suggested that EGR2 overexpression has a pivotal role in the downregulation of cytokines implicated in the pathophysiology of this acute neuropathy. ***The Journal of Immunology*****, 2016, 196: 1102–1107.**

Guillain-Barré syndrome (GBS) is an immune-mediated peripheral neuropathy involving both the myelin sheath and axons that affects the peripheral nervous system (1). It has been identified as the main cause of the acute neuromuscular paralysis worldwide, with an annual incidence ranging from 0.81 to 1.89 cases per 100,000 people (2). GBS is characterized by rapidly evolving ascending weakness, mild sensory loss, and hyporeflexia or areflexia, progressing to a nadir over up to 4 wk (2). Besides the classic presentation of ascending paralysis in demyelinating GBS, clinical variants are based on the types of nerve fibers involved (motor and/or sensory, cranial or autonomic), predominant mode of fiber injury (demyelinating versus axonal), and alterations in consciousness. Consequently, different subtypes of GBS such as acute inflammatory demyelinating polyneuropathy, Miller Fisher syndrome, acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN), acute pan-autonomic neuropathy, and Bickerstaff's brainstem encephalitis have been described previously (1–3).

Conventional treatment strategies for patients with GBS include plasmapheresis, i.v. Ig administration, and immunosuppressive drugs (2, 4). However, these treatments are relatively inefficient, invasive, and expensive (4). Therefore, it is necessary to implement new treatments to prevent both the development of the syndrome as well as the disability persistent in GBS patients.

Although GBS is considered to be an autoimmune disease with the involvement of both cellular and humoral immune responses (2), little is known about the molecular mechanisms involved in the pathogenesis of GBS and its variants (2, 5–9). Strong evidence support a role for Th17 and IL-17 response in GBS (5–9), and that axonal subtypes of GBS, AMAN, and AMSAN are caused by Abs to gangliosides on the axolemma that target macrophages to invade the axon at the node of Ranvier (2). About one-quarter of patients with GBS have suffered a recent bacterial or viral infection, and axonal forms of the disease are especially common in these patients (2, 10–14). The bacteria *Campylobacter jejuni* has been shown to have ganglioside-like structures in its LPS coat (10). Similar examples of molecular mimicry are seen with other organisms that trigger GBS such as *Haemophilus* bacteria and CMV (11). In addition, different types of viral hepatitis have been related to GBS (12). A high proportion of patients monoinfected or coinfected with the HIV and hepatitis C virus (HCV) develop GBS, pointing to an additive or synergistic effect of these two viruses on the peripheral nerve (13). Recent results showed that infection with one of these microorganisms leads to Ab production, which cross-reacts with gangliosides

*Hospital Nacional de Parapléjicos, Servicio de Salud de Castilla La Mancha, 45071 Toledo, Spain; [†]SaBio, Instituto de Investigación en Recursos Cinegéticos IREC-CSIC-UCLM-JCCM, 13005 Ciudad Real, Spain; [‡]Oh no sequences! Research Group, Era7 Bioinformatics, 18001 Granada, Spain; [§]Fundación Parque Científico de Madrid, 28049 Madrid, Spain; and [¶]Department of Veterinary Pathobiology, Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, OK 74078

[1]E.D.-P. and L.M.-H. contributed equally to this work.

ORCIDs: 0000-0002-2704-9782 (E.D.-P.); 0000-0002-7878-0786 (E.P.); 0000-0001-7032-8720 (R.T.); 0000-0002-5606-2767 (V.V.d.S.); 0000-0002-6331-9786 (R.R.); 0000-0001-5936-4018 (I.G.F.d.M.).

Received for publication September 29, 2015. Accepted for publication November 21, 2015.

This work was supported partially by European Union Framework Program 7 Antigone Project 278976. L.M.-H. was supported by a fellowship from the University of Castilla La Mancha (UCLM). M.V. was supported by the research plan of the UCLM.

E.D.-P. and J.d.l.F. conceived the experiments; E.D.-P., L.M.-H., E.P., A.G.-F., M.V., R.T., F.R.G., V.V.d.S., R.R., and I.G.F.d.M. performed the experiments; and J.d.l.F., E.D.-P., and E.P. wrote the paper. All authors approved the paper in its present form.

The RNA sequencing data presented in this article have been submitted to the National Center for Biotechnology Information's Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE72748) under accession number GSE72748.

Address correspondence and reprint requests to Dr. José de la Fuente, SaBio, Instituto de Investigación en Recursos Cinegéticos IREC-CSIC-UCLM-JCCM, Ronda de Toledo s/n, 13005 Ciudad Real, Spain. E-mail address: jose_delafuente@yahoo.com

The online version of this article contains supplemental material.

Abbreviations used in this article: AMAN, acute motor axonal neuropathy; AMSAN, acute motor sensory axonal neuropathy; Ct, cycle threshold; GBS, Guillain–Barré syndrome; HCV, hepatitis C virus; PGK1, phosphoglycerate kinase 1; SCI, spinal cord injury.