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Heterogeneity versus homogeneity of multiple sclerosis

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Abstract

The 10th International Congress of Neuroimmunology, including the 10th European School of Neuroimmunology Course, was held by the International Society of Neuroimmunology in Sitges (Barcelona, Spain) on 26–30 October 2010. The conference covered a wide spectrum of issues and challenges in both basic science and clinical aspects of neuroimmunology. Data and ideas were shared through a variety of programs, including review talks and poster sessions. One of the topics of the congress was whether multiple sclerosis is a homogenous or heterogenous disease, clinically and pathologically, throughout its course.

The 10th International Congress of Neuroimmunology, including the 10th European School of Neuroimmunology (ESNI) Course, was held by the International Society of Neuroimmunology (ISNI) in Sitges (Barcelona, Spain) from 26–30 October 2010. The conference was organized by President Caroline C Whitacre (Ohio State University, Columbus, OH, USA), Vice-President Tomas Olsson (Karolinska Institutet, Stockholm, Sweden), Secretary/Treasurer Trevor Owens (University of Southern Denmark, Odense, Denmark), and the local organizing committee in Barcelona, which consisted of five members: Pablo Villoslada (Hospital Clinic of Barcelona, Barcelona, Spain), Bernardo Castellano (Autonomous University of Barcelona, Bellaterra, Spain), Francesc Graus (Hospital Clinic of Barcelona, Barcelona, Spain), Isabel Illa (Hospital Sant Pau, Barcelona, Spain) and Xavier Montalban (Hospital Vall d'Hebron, Barcelona, Spain). The conference was composed of a series of six sessions: concurrent symposia, lectures, plenary symposia, poster sessions, workshops and training. There were 944 participants from all over the world. There were many discussions on neuroimmunology covering basic and clinical sciences and future directions in each session. In this article we will comment on several highlights of the meetings.

Current clinical studies of treatments for multiple sclerosis (MS) were reviewed by Stephen L Hauser (University of California, San Francisco, CA, USA) and Hans-Peter Hartung (Heinrich-Heine University, Dusseldorf, Germany). Immunomodulatory drugs, such as IFN- β and glatiramer acetate, have been widely used for treatment of MS and shown to be effective for relapsing–remitting (RR)-MS [1,2]. Recently, monoclonal antibodies against immune molecules, including T-cell and B-cell antigens, have been tested in clinical trials of MS. For example, an antibody against adhesion molecule very late antigen (VLA)-4 (natalizumab) has been shown to ameliorate RR-MS. Another intriguing monoclonal antibody that has been tested in RR-MS is ustekinumab, an antibody against the p40 subunit

that is a component of both IL-12 and IL-23. IL-12 and IL-23 contribute to the differentiation of Th1 and Th17 cells, respectively. It has recently been proposed that Th1 and Th17 cells are effector cells in MS pathogenesis. Recently, different dose injections of IL-12/23p40 neutralizing antibody, ustekinumab, have been tested in clinical trials of RR-MS to assess the drug's efficacy. However, the ustekinumab treatment failed to suppress disease activity of RR-MS at the primary end point for any dosage groups [3,4]. This contradicts our current theory of MS pathogenesis; the roles of Th1 and Th17 cells in RR-MS may be reconsidered in the future.

Rituximab, an anti-CD20 antibody specific for B cells, significantly ameliorated clinical signs in RR-MS. By contrast, this treatment was not effective against primary progressive (PP)-MS. Interestingly, however, a subgroup analysis of PP-MS showed that rituximab has a beneficial effect for patients with gadolinium-enhancing lesions, but not patients without gadolinium-enhancing lesions in MS [5]. The subgroup analysis suggests selective B-cell depletion may affect disease progression in patients with inflammatory lesions. In addition, these results may reflect possible heterogeneity of pathogenesis among PP-MS.

The heterogeneity of MS was also discussed by Wolfgang Brück (Georg-August University, Göttingen, Germany) based on neuropathological findings [6]. In studies on active demyelinating MS lesions, Brück and Lucchinetti classified MS lesions into patterns I to IV based on heterogeneity in immunopathological parameters, including T cells, macrophages, antibody and oligodendrocyte apoptosis, among patients (interindividual heterogeneity). In this classification, there is neither overlap of patterns nor a pattern change during the clinical course in individual patients (intraindividual homogeneity). The hypothesis of 'interindividual heterogeneity with intraindividual homogeneity' has been challenged by two groups [7]. First, Breij *et al.* found homogeneity in the lesions from MS patients suffering from the various courses of disease (interindividual homogeneity) [8]. All the active lesions had antibody, complement and macrophages associated with them; pattern II described by Lucchinetti *et al.* belongs to this category [6]. Second, Barnett *et al.* have proposed stage-dependent sequences of pathology in MS (intraindividual heterogeneity), since they found the presence of two different lesion types (patterns II and III) within one patient, which may represent the transition from the first stage of disease (oligodendrocyte apoptosis) to the second stage (T-cell-mediated inflammation) [9,10]. However, Brück supported intraindividual homogeneity of MS lesions, arguing that findings by Barnett *et al.* may not be from MS patients but from neuromyelitis optica, since neuromyelitis optica patients displayed lesions with both patterns II and III [9].

The meeting also highlighted the ongoing scientific discussion on how axonal damage occurs in MS [11,12]. Klaus-Armin Nave (Max Planck Institute, Göttingen, Germany) demonstrated evidence that oligodendrocytes support axonal functions independently of myelin [13,14]. The proteolipid protein 1 (*PLP1*)-null mice or 2',3'-cyclic-nucleotide 3'-phosphodiesterase (*CNP*)-deficient mice develop axonal degeneration with normal myelination. Since SIRT2 was absent in the myelin of *PLP^{null}* mice, SIRT2 may contribute to axonal preservation [15]. SIRT2 is a member of the sirtuin family and exhibits 27% sequence identity to SIRT1, a nuclear NAD-dependent deacetylase, implicated in the delay of Wallerian degeneration when activated by excess NAD synthesis [16].

Fumitaka Sato (Louisiana State University Health Sciences Center, Shreveport, LA, USA) tested whether treatment with resveratrol, a proposed SIRT1 activator, could be beneficial in two models for MS: experimental autoimmune encephalomyelitis (EAE) and Theiler's murine encephalomyelitis virus-induced demyelinating disease [17,18]. Unexpectedly, resveratrol treatment exacerbated clinical signs of both EAE and Theiler's murine encephalomyelitis virus-induced demyelinating disease. A lack of neuroprotective effect by

resveratrol in Sato's results is in accordance with recent reports that SIRT1 activation mediated by resveratrol was an assay artifact [19].

Iain L Campbell (University of Sydney, Sydney, Australia) presented a role of IL-6 via gp130, which is known to be a signal transducer for IL-6, in the regulation of astroglia and microglia function. Transgenic mice in which IL-6 production was restricted to the cerebellum developed severe ataxia after sensitization of myelin oligodendrocyte glycoprotein (MOG), while the MOG sensitization into wild-type mice caused classical EAE. The site-specific production of IL-6 increased infiltration of neutrophils into the cerebellum and decreased the expression levels of IFN- γ mRNA [20]. Astroglia and microglia activated by IL-6 have been thought to be linked to the differences. The IL-6-dependent gp130 pathway contributed to more severe neuroinflammation and neuronal injury by controlling the functions of astroglia and microglia.

John E Greenlee (University of Utah, Salt Lake City, UT, USA) presented the possible mechanism of cell death in paraneoplastic cerebellar degeneration by anti-Yo and anti-Hu antibodies, which react with cytoplasmic proteins of cerebellar Purkinje cells [21]. In cerebellar slice cultures, both antibodies were taken up by Purkinje cells, leading to cell death. Anti-Yo antibody was taken up by only Purkinje cells, while the incorporation of anti-Hu antibody was observed in all cerebellar neurons. Cell death mediated by anti-Yo antibody was not apoptosis, as the cell death was identified by neither terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling assay nor pancaspase antibody, although anti-Hu antibody induced apoptosis.

President Whitacre demonstrated the relationship between pregnancy and MS. During pregnancy, MS has been reported to be ameliorated, although the exact mechanism is unclear. Whitacre demonstrated that exosomes in serum isolated from pregnant mice downregulated inflammation and induced neuro-protection in mice with EAE *in vivo* [22]. The exosomes derived from pregnant mice also suppressed T-cell proliferation *in vitro*, which related to inflammatory responses and neurodegeneration. These data will provide insight into possible therapeutic interventions using exosomes in MS.

Information resources

- 10th International Congress of Neuroimmunology, Sitges (Barcelona, Spain), www.isni2010.org/index.php
- Special Issue: 10th International Congress of Neuroimmunology. ISNI 2010 Abstracts. *J. Neuroimmunol.* 228(1–2), 1–220 (2010).

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