Intravenous Immunoglobulins Lower Inflammatory Gene Expression in Skin Biopsies of Chronic Inflammatory Demyelinating Polyradiculoneuropathy Patients

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Dear Sir,

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is the most common form of chronic autoimmune neuropathy [1]. The underlying immune-mediated mechanisms have not yet been fully elucidated [2], but gene expression analyses identified inflammatory molecular markers that are upregulated in skin nerve biopsies [3, 4]. Intravenous immunoglobulins (IVIG) are a first-line therapy for CIDP [5]. In order to gain insight in the anti-inflammatory effects of IVIG, 2 subgroups of patients treated with either IVIG or other immunosuppressive agents were selected from a previous gene expression profiling study [4]. The selected subgroups were further studied using a transcriptional microarray analysis in skin punch biopsies.

Four patients (‘IVIG’ group) were treated with Privigen® (2 g/kg administered over 5 days) 2–6 months before skin biopsy was performed. Three patients (‘NoIVIG’ group) received other treatments: prednisone (30 mg/day), azathioprine (2 mg/kg/day) or tacrolimus (2 mg/day), respectively. All 7 patients had stable active disease according to CIDP Disease Activity Status (CDAS) [4, 6]. Twelve healthy volunteers were used as controls (‘Ctrl’ group). Skin punch biopsies were performed 10 cm above the external malleoli and snap frozen in liquid nitrogen. RNA extraction, gene expression profiling, and MetaCore® data analysis were performed according to the methods described previously [4] with the following filters: fold expression change >1.15, p < 0.05, Y chromosome linked genes and duplicate removal. Data analysis was made according to a 3 set comparison (C), where C1 stands for ‘IVIG vs. Ctrl’, C2 for ‘IVIG vs. NoIVIG’, and C3 for ‘NoIVIG vs. Ctrl’. This study was approved by the local Ethics Committee (protocol 235/10).

We first analyzed the total number of differentially regulated genes between the 3 groups. Results showed 223 differentially regulated genes between patients treated with IVIG and the control group (C1; fig. 1a). In contrast, numbers of differentially regulated genes were much higher when comparing NoIVIG patients to IVIG and the control group respectively: 1117 genes were differentially regulated between patients treated with IVIG vs. NoIVIG (C2) and 1022 genes were differentially regulated between NoIVIG vs. controls (C3) (online suppl. tables C1, C2 and C3, see www.karger.com/doi/10.1159/000447127).

A downregulation of genes involved in inflammation, tissue remodeling and wound repair and cell-cycle regulation such as ULK3 (control of autophagy), TRAP1 (stress regulation), ANAPC11 (cell-cycle regulation), CEBPA (transcription factor), PDRG1 (inflammation), PFKL (AKT signaling), and NCS1 (calcium sensor) was found in IVIG-treated patients (fig. 1b). All these genes were downregulated in IVIG-treated patients (comparisons C1 and C2) but not in the non-IVIG-treated subgroup (comparison C3). In addition, in comparison to C2, IVIG treatment was found to downregulate AKT (fold change = –1.38, p = 0.01) as well as its downstream partners CyclinD1 and CDK4, which are the key regulators of the cell cycle.

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Taken together, our results suggest that IVIG-treated patients have a gene profile (fig. 1a) that is more similar to that of healthy subjects than that of patients treated with other immunosuppressants. In addition, our data show the downregulation of genes involved in inflammation and proliferation (fig. 1b), genes previously reported to be upregulated in active CIDP [3, 4]. Of particular interest, is the downregulation of AKT, a key cell-cycle regulator [7] and its downstream partners CyclinD1 and CDK4 by IVIG therapy. This suggests a lower activity of cell proliferation in patients treated with IVIG compared to other immunosuppressants. Based on this finding, and on reports that IVIG inhibits T-cell proliferation [8], we speculate that IVIG therapy may inhibit T-cell proliferation in inflamed nerve fibers in CIDP patients [2]. Lower maintenance doses of non-IVIG immunosuppressants used to treat our CIDP patients may explain why these agents were not shown to lower inflammatory expression in our study. The fact that all patients had stable active disease according to their CDAS score independent of treatment argues against a disease-related confounding effect. Whether the timing of skin biopsy influences these observations remains to be demonstrated in a larger cohort of patients.

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Statement of Ethics

The study has been approved by the Ethics Committee.

Disclosure Statement

There is no conflict of interest in relation to this work.

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